Shedding light on depressive, anxiety and sleep disorders in Parkinson's disease

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SHEDDING LIGHT
ON DEPRESSIVE, ANXIETY AND SLEEP DISORDERS IN PARKINSON'S DISEASE

Sonja Rutten

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Chapter 1

General Introduction

Background

Parkinson's disease (PD) is a neurodegenerative disorder, with an estimated prevalence of 1,350 per 100,000 in the Netherlands (1). The disease is best known for its characteristic motor symptoms: brady- and hypokinesia, rigidity, tremor and postural instability. However, the disease is also accompanied by a variety of non-motor symptoms, including autonomic failure, cognitive dysfunction, sleep disturbances and neuropsychiatric disorders (2).

According to Braak's hypothesis (3), PD is caused by a neuropathological process that predominately progresses in a caudal to rostral direction through the central nervous system, from the lower brainstem and olfactory system, via the basal ganglia and thalamus, to the cortex. The characteristic motor symptoms of PD develop when approximately 50% of the dopaminergic neurons in the substantia nigra have degenerated (3). In addition, due to neuropathological involvement of other areas of the brain, non-motor symptoms are highly prevalent throughout the course of the disease, from the prodromal phase until the end stage of PD (3, 4). Autonomic failure in PD is mainly associated with brainstem pathology and includes disturbances in the regulation of blood pressure, gastrointestinal and urogenital functions (5). Cognitive impairment in PD initially involves executive disturbances, visuospatial dysfunction and working memory deficits, while episodic memory remains relatively unaffected (6). At the time of diagnosis, about 15% of PD patients already fulfil criteria for Mild Cognitive Impairment (MCI) (7). MCI is defined as a gradual cognitive decline as experienced by the patient or observed by an informant or clinician, supported by the presence of cognitive deficits on neuropsychological testing, but insufficient to interfere significantly with functional independence (6). MCI is a predictor of PD dementia (PDD), with an annual conversion rate from MCI to PDD of approximately 11% (8).

PD-associated neuropsychiatric disorders include psychosis, apathy, anxiety, depression and impulse control disorders (ICD) and other PD-related impulsive-compulsive behaviors (ICBs) (9). Neuropsychiatric disorders in PD have a multifactorial etiology: they result from a combination of psychological, social and neurobiological factors. Anxiety and depression can be partially viewed as a reaction to receiving the diagnosis of an incurable, progressive disease like PD, and the development of disabling motor and non-motor symptoms leading to loss of independent functioning. However, the neurochemical changes resulting from the neurodegenerative process also play an important causal role. In neuroimaging studies, the presence and severity of depression and anxiety in PD were associated with mesolimbic dopaminergic degeneration (10). In addition to the dopaminergic system, the noradrenergic, serotonergic and cholinergic systems are also involved in the pathophysiology of these neuropsychiatric disorders (10). Moreover, PD patients are prone to a disturbance of their circadian rhythm, which is a risk factor for depression and sleep disorders (11, 12).

Sleep, anxiety and depression in PD

Sleep disturbances are common in PD patients, varying from excessive daytime sleepiness to insomnia (13). More than half of all PD patients experience insomnia, with sleep fragmentation and early morning awakening being more common than problems with sleep initiation (14), whereas excessive daytime sleepiness occurs in 20 – 60% (13). Specific sleep-wake disorders, like Rapid Eye Movement (REM) sleep behavior disorder (RBD) and restless legs syndrome, occur more frequently in PD patients than in the general population (15, 16). In RBD, there is a loss of physiological atonia during REM-sleep, resulting in dream enactments. These dream enactments can be violent in nature and hence result in injury of either the patient or his/her bed partner (15). Sleep disorders in PD are not only associated with fatigue, daytime sleepiness and an increased risk of car accidents due to 'sleep attacks', they also have a significant impact on quality of life and the severity of motor and non-motor symptoms (13).

Anxiety disorders occur in approximately one-third of PD patients (17), with about 12% having multiple comorbid anxiety disorders (18). Anxiety in PD is associated with more severe motor and non-motor symptoms (19, 20) and a decreased health-related quality of life (21-23). Generalized anxiety disorder, social phobia and specific phobias are the most common anxiety disorders in PD patients (17). However, a substantial number of PD patients experience clinically relevant symptoms of anxiety without fulfilling criteria for a specific anxiety disorder as defined in the Diagnostic and Statistical Manual of mental disorders (DSM) (17, 18).

Clinically relevant depressive symptoms are experienced by approximately one third of PD patients, with an estimated prevalence of major depressive disorder (MDD) of 17% (24). According to the DSM-5, MDD is characterized by a depressed mood and/or loss of interest or pleasure (see Table 1) (25). Depression in PD is associated with a more rapid deterioration of motor and cognitive functioning, greater disability and a higher mortality rate (26-29). Moreover, depression is the most important neuropsychiatric symptom influencing health-related quality of life in PD patients (30).

Table 1: DSM-5 criteria for Major Depressive Disorder (25)

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective reports or observation made by others;
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day;
3. Significant weight loss when not dieting or weight gain, or a decrease or increase in appetite, nearly every day;
4. Insomnia or hypersomnia, nearly every day;
5. Psychomotor agitation or retardation, nearly every day;
6. Fatigue or loss of energy, nearly every day;
7. Feelings of worthlessness or excessive or inappropriate guilt, nearly every day;
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day;
9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

D. The occurrence of the major depressive episode is not better explained by a schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorder.

E. There has never been a manic episode or a hypomanic episode.

Cross-sectional studies provide evidence for a positive association between insomnia, depression and anxiety (31-34), and anxiety and depression co-occur in approximately 40% of PD patients (35). Moreover, these neuropsychiatric symptoms show overlap with other PD-related dysfunctions. For example, trembling, perspiration and dizziness can be attributed to motor or autonomic failure in PD patients, but may also be symptoms of a panic attack. This symptom overlap makes the diagnostic process in PD patients more difficult, which may contribute to both under- and overdiagnosis of anxiety and depression in daily clinical practice (36, 37). To complicate things even further, motor and psychiatric symptoms in PD have a reciprocal influence. For example, the re-emergence of motor symptoms in the OFF phase can have a substantial psychological impact, whereas the visibility of motor symptoms can contribute to the development of social anxiety (23, 38). Vice versa, anxiety and depression are associated with an increase in motor symptoms, like freezing of gait (39). In addition, the treatment of one PD-related symptom can have a negative impact on another. For example, treatment with antidepressant medications can worsen motor symptoms (40). A clinician treating PD patients should therefore have a holistic view of both diagnosis and treatment, and collaborate closely with other (para)medical professionals in the case of possible symptom overlap and conflicting treatment effects. A better understanding of anxiety, depression and sleep disorders, their interaction and relationship with other PD-related disturbances, will contribute to improved recognition, diagnosis and treatment of these disorders in PD patients.

Treatment

In daily clinical practice, MDD in PD is commonly treated with antidepressants, including Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Noradrenalin Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), and MAO Inhibitors (MAOIs). A recent meta-analysis by Zhuo et al. (2017) demonstrated a significantly larger reduction of depression scores as compared to placebo for all antidepressants except for the MAOIs (41). Moreover, several randomized-controlled trials (RCTs) demonstrated a positive effect of dopamine agonists on mood and motivational symptoms in PD patients (42, 43). A potential negative adverse effect of dopamine agonists, however, is the development of ICD and ICBs (44).

To date, there are no RCTs in PD patients on the pharmacological treatment of anxiety as a primary outcome measure. However, one RCT studying the effects of antidepressants on anxiety as a secondary outcome measure suggests a positive effect of TCAs (45).

The pharmacological treatment options for sleep disturbances in PD depend on its causes. For example, poor sleep due to an overnight increase in parkinsonism may improve with slow-release formulations of either levodopa or dopamine agonists, while insomnia associated with depression can be ameliorated with adequate antidepressant treatment

(46). While sleeping pills are frequently prescribed for insomnia in PD patients (32), only one RCT on their efficacy was published, showing a positive effect of eszopiclon on the number of awakenings and sleep quality (47). For the treatment of RBD, there is evidence for a positive effect of clonazepam and exogenous melatonin (48).

Unfortunately, all pharmacological treatment options have potential adverse effects. Nausea, somnolence and orthostatic hypotension are reported by PD patients as adverse effects of both antidepressants and dopamine agonists (49). Moreover, dopamine agonists can provoke hallucinations, ICD and ICBs, while antidepressants can have anticholinergic effects which can negatively impact cognitive functioning, and might worsen motor function (40, 41, 49). Benzodiazepines prescribed for insomnia carry a risk of dependency and an increased propensity to falls (50). Moreover, adding extra medications can decrease overall treatment adherence in PD patients (51, 52) and polypharmacy carries the risk of unfavourable interactions. Therefore, non-pharmacological interventions, like light therapy (LT), transcranial magnetic stimulation (TMS) and psychotherapy have become increasingly popular.

The scientific evidence for the efficacy of LT is reviewed in **Chapter 6**. A systematic review on the effects of TMS on depression and cognition in PD by Dinkelbach et al. (2017) showed a positive effect of repetitive TMS of the dorsolateral-prefrontal cortex on mood (53). One case series on the effects of electroconvulsive therapy (ECT) in PD showed promising results on both motor function and mood (54), but no further efficacy studies in PD patients with MDD have been conducted. The efficacy of psychotherapy, especially Cognitive Behavioral Therapy (CBT), for depression, anxiety and insomnia in PD patients is supported by an increasing amount of evidence (40, 46, 55). However, for PD patients with cognitive dysfunction, psychotherapy may not be a feasible treatment option.

Overall, there is insufficient evidence to support the efficacy of either pharmacological or non-pharmacological treatment options for depression, anxiety and sleep disorders in PD patients. More well-designed RCTs with a larger study sample and a longer study duration are needed before we can make strong evidence-based recommendations for the treatment of these disorders. Due to the potential adverse effects of drug therapy and the risks of polypharmacy, more research on the feasibility and efficacy of non-pharmacological treatment options in PD patients is needed.

Aims and outline of this thesis

This thesis can be divided into two parts. *Part 1* aims at gaining a better understanding of anxiety, depression and sleep disorders in PD, their interaction with one another and with other PD-related disturbances, providing potential starting points for the improvement of the diagnostic process in clinical practice. *Part 2* focuses on the effects of non-pharmacological treatment options for anxiety, depression and sleep disorders in PD patients, including psychological interventions and LT.
To gain more insight in the phenomenon of anxiety in PD, we start *Part 1* of this thesis with a cross-sectional study on anxiety in 294 PD patients, as reported in **Chapter 2**. We performed a principal component analysis to explore the underlying 'factors' or symptom dimensions of anxiety covered by the Beck Anxiety Inventory (BAI) (56). The dimensionality of the BAI in PD patients was studied before by Leentjens et al. (2008), but no satisfactory factor solution could be found, probably due to heterogeneity of the study sample (57). In this chapter, we describe the different symptom dimensions of anxiety, as well as their relatedness to depression, autonomic dysfunction and motor disability.

Since better knowledge of the risk factors for the development of anxiety in PD can facilitate the recognition of anxiety in daily clinical practice, we studied predictors of anxiety in patients with early-stage PD in **Chapter 3** (58). With the exception of one longitudinal study assessing the effect of the initiation of dopamine replacement therapy on the course of neuropsychiatric symptoms in PD (59), all previous studies on predictors of anxiety in PD had a cross-sectional design. In **Chapter 3**, we describe the results of a longitudinal study using data from the Parkinson's Progression Markers Initiative (PPMI), an international prospective cohort study that aims to identify markers for the progression of PD. We assessed the predictive value of 20 different demographic and clinical characteristics for the course of symptoms of anxiety during two years follow-up in a subsample of PD patients that were not using any psychopharmacological agents at baseline.

The results of the studies described in **Chapters 2 and 3** show a close relationship between anxiety, depression and insomnia in patients with PD. However, this does not necessarily imply a temporal relationship in the course of their development. Based on previous studies in non-PD samples, two hypotheses were postulated. The first hypothesis, based on two epidemiological studies in the general population, in which anxiety and depression were found to precede insomnia, holds that affective disorders increase the risk of sleep disturbances (60, 61). However, other population-based studies suggest that insomnia increases the chance of developing an anxiety or depressive disorder (62, 63), giving rise to the second hypothesis, namely that insomnia is a risk factor for the development of an anxiety and depression in PD patients (60, 64-66). In **Chapter 4**, we report the results of the first longitudinal study on the temporal relationship between depression, anxiety and insomnia in PD patients, exploring both hypotheses (67). For this study we used data obtained during the first six months of follow-up in a subsample of PD-medication naïve patients of the PPMI cohort.

In *Part 2* of this thesis, we shift focus from screening and diagnostics to treatment. As discussed previously, psychological interventions are an attractive alternative to pharmacological treatment of depression and anxiety in PD patients. Previous meta-analyses have shown a positive effect of CBT on anxiety and depression in PD (40, 55). In the last couple of years, mindfulness-based treatments (MBTs) are increasingly popular. However, up to this date, no meta-analysis has described the effects of MBTs on depression or anxiety in PD patients. In **Chapter 5** we describe a meta-analysis of the available literature on the effects of both CBT and MBTs on psychological distress, including symptoms of depression and anxiety, in patients with PD, Huntington's disease and multiple sclerosis (68). These three neurodegenerative disorders are thought to have a similar response to psychotherapeutical interventions since they are all progressive neurological diseases with a reciprocal interaction between physical symptoms and psychological distress.

Chapter 6 introduces a new treatment option for insomnia and depression in PD. In this chapter, we introduce the hypothesis that circadian dysfunction is a common underlying factor for the frequent (co-)occurrence of insomnia and depression in PD (69). In PD patients, a variety of factors can negatively influence the circadian system, resulting in desynchronization of the patient's circadian rhythm with his or her environment, which is a known causal factor in the development of insomnia and mood disorders (11, 12, 70). In **Chapter 6**, we discuss the various factors that make PD patients prone to a desynchronization of the circadian rhythm, and hence the option of using LT to improve sleep and mood by a restoration of the circadian rhythm.

Although the results of previous studies are promising (71-74), no RCT on the effects of LT on either motor or non-motor symptoms in PD had been performed up to 2012. In **Chapter 7**, we present the results of a multicenter RCT on the safety and effectiveness of Spectramax LT as an adjunctive treatment for PD. In this study, 92 participants were randomized to Spectramax LT (blue/green LED light, 950 lux) or control LT with a bandwidth and intensity not expected to influence the circadian rhythm (white LED light, 100 lux). The Spectramax LT device was specifically designed for the treatment of PD patients. Blue light is more effective than white light in the suppression of melatonin secretion and the shift of circadian rhythms (75, 76), but PD patients may be less sensitive to blue light due to yellowing of the lens and other conditions associated with advancing age (77). The Spectramax LT device was therefore designed to emit narrow band blue/green light. The primary outcome of this RCT was the change in severity of PD, as measured with the composite score of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I, II and III. Secondary endpoints included sleep, neuropsychiatric symptoms, individual MDS-UPDRS components and quality of life.

In the next two chapters, we zoom in on the effects of LT on depression in PD. **Chapters 8 and 9** demonstrate the study design and results, respectively, of an RCT studying the efficacy of LT on depressive symptoms, as compared to a control condition (78, 79). In the clinical trial presented in **Chapter 9**, we randomized 83 PD patients with PD and MDD to treatment with Bright LT (daylight spectrum light, 10,000 Lux) or a control light (daylight spectrum light, 200 Lux). The primary outcome of the study was the Hamilton Depression Rating Scale (HDRS). Secondary outcomes were objective and subjective sleep measures and salivary melatonin and cortisol concentrations.

The final chapter, **Chapter 10**, provides a summary of the findings and a review of all study results in the context of the existing literature. This chapter includes a discussion of the methodological limitations and the clinical implications of our study findings, and highlights potential future directions for research on depression, anxiety, sleep disorders and circadian dysfunction in PD.

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2

Chapter 2

Anxiety in Parkinson's disease: symptom dimensions and overlap with depression and autonomic failure

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Abstract

Introduction

Anxiety disorders are highly prevalent in patients with Parkinson's disease (PD) and have a major impact on wellbeing. They nevertheless receive limited scientific attention. This study aimed to establish the symptom dimensions of anxiety in PD, and their relationship with depression, autonomic failure and motor symptoms.

Methods

In this cross-sectional observational study, symptoms of anxiety were measured with the Beck Anxiety Inventory (BAI) in 294 PD patients. Symptom dimensions of anxiety in PD were explored through principal component analysis (PCA) of BAI items. The relationship between anxiety and depressive, autonomic and motor symptoms was assessed through PCA and regression analyses.

Results

Clinically relevant symptoms of anxiety were present in 45% of patients. PCA of the BAI resulted in five subscales, corresponding to a single affective and four somatic symptom dimensions (*thermoregulation, hypotension, hyperventilation* and *trembling)* of anxiety. Symptoms of anxiety and depression displayed a large overlap. All somatic BAI subscales were significantly influenced by motor and autonomic symptoms, while the affective subscale was not.

Conclusion

Anxiety in PD comprises affective and somatic symptom dimensions. The affective subscale of the BAI is not influenced by motor or autonomic symptoms, and may therefore prove useful for future research. Scores on the somatic subscales of the BAI were associated with autonomic failure and motor impairment, demonstrating a strong interplay between motor and non-motor symptoms in PD. These results stress the importance of a holistic approach of anxiety in PD.

Introduction

Despite a high prevalence and a major impact on daily functioning and quality of life in patients with Parkinson's disease (PD), anxiety has only recently attracted scientific attention. Estimates suggest that 40-50% of PD patients experience clinically relevant symptoms of anxiety (1, 2), and approximately one third suffers from an anxiety disorder as specified by the Diagnostic and Statistical Manual of mental disorders (DSM) IV-TR criteria (1-4). Generalized anxiety disorder, social phobia and anxiety disorder not otherwise specified (NOS) are most frequently diagnosed in this population (2, 3, 5). Anxiety disorders are more common in PD patients than in the general population, in primary care clinics or in patients with other chronic medical conditions, where prevalence rates vary between 5 and 11% (4). Anxiety in PD patients is associated with increased subjective motor symptoms (6), more severe gait problems (7), dyskinesias (7), freezing (8), motor response fluctuations (6), and a decrease in health-related quality of life (9).

In clinical practice, anxiety disorders are often underdiagnosed in PD patients (10). In a large proportion of patients with PD that report clinically relevant anxiety, the symptoms do not meet the criteria of a discrete DSM-IV disorder and are therefore classified as an anxiety disorder NOS (3). This suggests that anxiety disorders may have an atypical presentation in this population. The poor recognition of anxiety might also be explained by the overlap and interaction with PD-related motor and non-motor symptoms, such as depression, motor symptoms and autonomic failure.

An improvement of the diagnostics of anxiety in PD could be aided by an in-depth study of the symptom dimensions covered by self-report questionnaires such as the Beck Anxiety Inventory (BAI) (11) and their relatedness to other motor and non-motor symptoms. Factor analysis is a statistical technique that can help to explore the underlying factors or symptom dimensions covered by a questionnaire. In non-PD samples factor analysis has shown that the BAI comprises cognitive and somatic factors and that the BAI is able to differentiate between symptoms of anxiety and depression (12, 13). Dimensionality of the BAI in PD patients was only addressed in a single study (14), but no satisfactory factor solution was found, possibly due to the heterogeneity of the study sample.

In the present study, we analysed the symptom dimensions of the BAI within a large sample of PD patients. Secondly, we assessed the overlap of symptoms of anxiety with depression, autonomic dysfunction and motor disability in PD.

Methods

Subjects

For this cross-sectional study, we used data collected during routine clinical assessments at the outpatient clinic for movement disorders of the VU University medical center (VUmc) in Amsterdam, the Netherlands, between May 2008 and January 2013. In this period, 383 PD patients were assessed. Patients were clinically diagnosed with idiopathic PD using the United Kingdom PD Society Brain Bank (UKPDSBB) criteria. The clinical diagnosis was supported by both magnetic resonance imaging (MRI) and dopamine transporter single-photon emission computed tomography (DAT-SPECT) scans in 244 patients, by MRI only in 37 patients and by DAT-SPECT scan only in 23 patients. In the remaining 79 patients, no brain imaging was performed. All included patients gave written informed consent to use their clinical data for scientific purposes. Patients with severe cognitive decline, defined as a Mini Mental State Examination (MMSE) score < 24, were excluded.

Measurements

Anxiety

Symptoms of anxiety were measured with the BAI. The BAI is a 21-item self-report instrument asking for symptoms of anxiety over the past week (11). Patients answer on a four-point Likert scale, ranging from 0 (not at all) to 3 (severely). In patients with PD, clinically relevant anxiety is defined as a BAI-score > 12 (14). This cut-off score is lower than in the general population, due to a lower construct validity of the BAI in PD patients (14).

Clinical and demographic factors

Age, gender and the use of dopaminergic medication (0 = no, 1 = yes) were registered for use in statistical analyses. The independent variables of major interest were symptoms of depression, motor dysfunction and autonomic failure. We evaluated symptoms of depression with the Beck Depression Inventory (BDI) (15). Severity of motor symptoms was assessed using section III and V (Hoehn and Yahr stage) of the Unified Parkinson Disease Rating Scale (UPDRS) (16). We used the Scales for Outcomes in Parkinson's disease – Autonomic (SCOPA-AUT) (17) to assess autonomic failure. The SCOPA-AUT includes five questions on sexual function: item 22, 23 and 23a apply to men, and item 24 and 25 to women. The answers to these questions were unreliable on multiple occasions, e.g. patients choosing "not applicable" for all five items, or male patients answering question 24 or 25. Therefore, we decided to exclude the sexual items of the SCOPA-AUT from the analyses.

Statistical analyses

We performed all analyses using IBM SPSS Statistics 20 for Windows. The significance level was set at $p < 0.05$ with two-sided testing. Acceptability of missing values on the BAI, BDI and SCOPA-AUT was determined as less than 16.67% of items. In the event of more missing data, we excluded the patient for the analysis by pair-wise exclusion. When less than 16.67% of data was missing, we filled in missing values by mean imputation. We performed no imputation of missing data on the UPDRS-III, since we considered this to be unreliable for this scale.

In the first analysis, we assessed dimensionality of the BAI with a principal component analysis (PCA). To determine the number of extracted factors we combined the Cuttman-Kaiser Eigenvalue greater-than-one rule and the "scree plot" criterion. We used oblimin rotation because we expected the different factors to correlate with each other. The factors obtained in this analysis can be considered as subscales of the BAI or symptom dimensions of anxiety. Scores on the derived subscales of the BAI were used in further analyses.

Second, we studied the relationship between the BAI, BDI, SCOPA-AUT and UPDRS-III, by conducting multiple linear regression analyses. Assumptions for regression analyses (normality and homoscedasticity of residuals) were checked. Multicollinearity was evaluated with a correlation matrix and calculation of the variance inflation factor (VIF).

The total BAI score was the dependent variable in the first set of regression analyses. In the second set, it was the score on the subscale of the BAI, derived with PCA previously. The independent variables of interest were the total score on the BDI, SCOPA-AUT and UPDRS-III. We conducted all analyses first with only the independent variable of interest (unadjusted model). We then adjusted the model stepwise for age and gender (model 1), use of dopaminergic medication (model 2), and the other two independent variables of main interest, i.e. the BDI, SCOPA-AUT and/or UPDRS-III score (model 3). Finally, we examined confounding in all models.

Results

Of the original sample of 382 PD patients, 75 patients met exclusion criteria (MMSE < 24). An additional 13 patients were excluded from the analyses for not meeting our standards of acceptability of missing values on the BAI. This resulted in a total sample size of 294 patients. Due to missing data on the BDI, UPDRS-III and/or SCOPA-AUT, 3 to 18 additional patients were excluded pair-wise during statistical analyses. The majority of patients was male. Mean age was 64.5 years. Patients had a mean UPDRS-III score of 25.8 and a median Hoehn and Yahr stage of 2. Demographic and clinical characteristics of the sample are given in Table 1.

Table 1: **Demographic and clinical characteristics of subjects (n = 294).**

	Mean	SD	Range
% Female	39.5		
Age	64.5	10.3	27 - 89
Disease duration (yr)	5.1	5,6	0 - 40
MMSE score	28.0	1.7	24 – 30
BDI score	11.4	8.0	0 – 36
SCOPA-AUT score	35	10.0	0 - 64
UPDRS-III score	25.8	12.3	2 - 58
Hoehn &Yahr stage	2 (median)		1 - 5
% use dopaminergic medication	48.6		

MMSE = Mini Mental State Examination, BDI = Beck Depression Inventory, SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; UPDRS = Unified Parkinson's disease Rating Scale

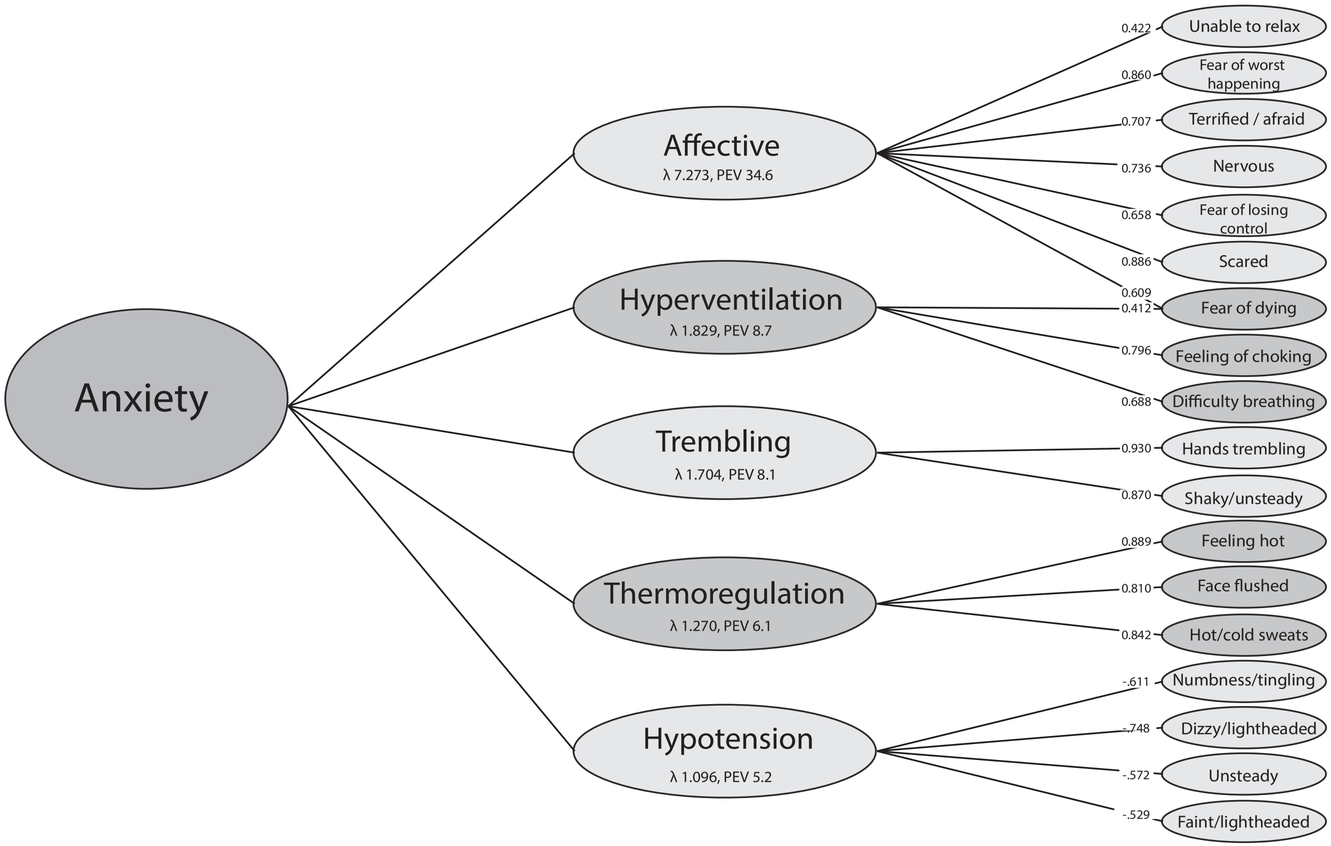
Occurrence and symptom dimensions of anxiety in PD

The mean score on the BAI was 14.2 (SD 9.8, range 0 - 50). Forty-five percent of patients in our sample had a BAI score of 12 or more, which is considered to be a clinically relevant level of anxiety (14).

The Eigenvalue > 1 criterium suggested that five factors should be extracted. This was confirmed by an inspection of the scree plot (see Figure S1 in the supplementary material). Items 3 'wobbliness in legs', 7 'heart pounding/racing' and 18 'indigestion' had a loading of less than 0.4 on all factors and were therefore excluded from the factor solution.

The five obtained factors were interpreted as *anxiety*, *thermoregulation, hypotension, hyperventilation* and *trembling*. The factor solution explained 62.7% of variance. Figure 1 demonstrates the distribution of the BAI items over the five factors, with corresponding factor loadings.

Figure 1: **Graphical display of the Exploratory Factor Analysis solution of the BAI. Factor loadings, Eigenvalues (λ) and percentage of explained variance (PEV) are displayed.**



Associations between anxiety, depression, motor dysfunction and autonomic failure in PD

Histograms demonstrated that the residuals of both the total BAI score and subscales of the BAI had a positively skewed distribution. Transformation of the data did not improve normality. To maintain interpretability of results, we decided to use the original data for the analyses. Homoscedasticity was confirmed by plotting the regression standardized predicted value against the regression standardized residual. Both the correlations (see Table 2) and the VIF (ranging from 1.005 to 1.610) indicated non-collinearity of the data.

Results of the multiple regression analyses with the BAI total score and subscales of the BAI as dependent variable are presented in Table 3. In this table, the final, adjusted models are displayed, showing the influence of each independent variable on the outcome variable. The unadjusted and adjusted models, including detailed information on confounding, can be found in Supplementary Table S1.

Table 2: **Matrix of the Pearson's correlation coefficients (r) for the BAI, BDI, SCOPA-AUT, UPDRS-III and age.**

	BAI	BDI	SCOPA-AUT	UPDRS-III	age
BAI	1.000	0.735**	0.616**	0.234**	0.100
BDI	0.735**	1.000	0.535**	0.230**	0.120*
SCOPA-AUT	0.616**	0.535**	1.000	0.330**	0.277**
UPDRS-III	0.234**	0.230**	0.330**	1.000	0.300**
age	0.100	0.120*	0.277**	0.300**	1.000

* p-value < 0.05, ** p-value < 0.01 (2-tailed)

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory, SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; UPDRS = Unified Parkinson's disease Rating Scale

The BAI total score was significantly influenced by age and gender: younger patients and females had a higher score on the BAI than older patients and men. The BAI score also increased with a higher score on the BDI and SCOPA-AUT. The UPDRS-III score no longer significantly influenced the BAI score after adjustment for score on the BDI and SCOPA-AUT.

All subscales of the BAI were influenced by the BDI score. Moreover, the subscales *thermoregulation* and *hyperventilation* were significantly influenced by the SCOPA-AUT, the *trembling* subscale by the UPDRS-III, and the *hypotension* subscale by both. The *affect* subscale was only significantly influenced by the BDI score, and not by the SCOPA-AUT and UPDRS-III.

Table 3: **Results of multiple linear regression analysis of the BAI total score and score on subscales of the BAI with the BDI, SCOPA-AUT and UPDRS-III. Regression coefficients (B) with 95% confidence intervals (95%-CI of B), standardized regression coefficients (β) and significance (indicated with *) are displayed for the final model.**

Independent variable →	***BAI total score***			***Subscale Affective***			***Subscale Thermoregulation***		
Dependent variable ↓	**B**	**95%-CI of B**	**β**	**B**	**95%-CI of B**	**β**	**B**	**95%-CI of B**	**β**
(Constant)	-1.053	-6.086 – 3.979		1.968	-.648 - 4.584		1.074	-.360 – 2.508	
BDI	0.688	0.582 – 0.794	0.560***	0.373	0.318 – 0.428	0.678***	0.050	0.020 – 0.080	0.193**
SCOPA-AUT	0.397	0.294 – 0.501	0.352***	0.046	-.008 – 0.100	0.092	0.098	0.069 – 0.128	0.416***
UPDRS-III	0.026	-.037 – 0.089	0.033	-.010	-.043 – 0.022	-.029	-.005	-.023 – 0.013	-.031
Gender	-2.198	-3.666 – -.730	-.110**	-.682	-1.445 – 0.081	-.076	-.488	-.906 – -.070	-.116*
Age	-.082	-.156 – -.007	-.086*	-.028	-.067 – .010	-.067	-.050	-.072 – -.029	-.253
Use of dopaminergic medication	-1.457	-2.959 – .045	-.074	-.890	-1.671 – -.110	-.101*	0.159	-.268 – 0.587	0.039
R^2		0.629			0.499			0.311	

* p-value <0.05, ** p-value < 0.01, *** p-value < 0.001; R2 = proportion variance of independent variable explained by the regression model

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory, SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; UPDRS = Unified Parkinson's disease Rating Scale

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Table 3, continued

Independent variable →	Subscale Trembling			Subscale Hyperventilation			Subscale Hypotension		
Dependent variable ↓	**B**	**95%-CI of B**	**β**	**B**	**95%-CI of B**	**β**	**B**	**95%-CI of B**	**β**
(Constant)	-.828	-2.144 – 0.487		-1.004	-1.680 – -.329		-1.890	-3.373 – -.406	
BDI	0.056	0.029 – 0.084	0.256***	0.022	0.008 – 0.036	0.191**	0.105	0.074 – 0.136	0.335***
SCOPA-AUT	0.024	-.003 – 0.051	0.117	0.040	0.026 – 0.054	0.374***	0127	0.096 – 0.157	0.441***
UPDRS-III	0.027	0.011 – 0.044	0.189***	-.001	-.010 – 0.007	-.016	0.019	0.001 – 0.038	0.094*
Gender	-.163	-.547 – 0.221	-.045	0.076	-.121 – 0.273	0.040	-.476	-.908 – -.043	-.093*
Age	0.019	0.000 – 0.039	0.112	-.004	-.014 – 0.006	-.042	-.009	-.031 – 0.013	-.037
Use of dopaminergic medication	-.547	-.939 – -.154	-.156*	0.076	-.125 – 0.278	0.041	-.157	-.599 – 0.286	-.031
R^2		0.208			0.255			0.502	

* p-value <0.05, ** p-value < 0.01, *** p-value < 0.001; R2 = proportion variance of independent variable explained by the regression model

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory, SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; UPDRS = Unified Parkinson's disease Rating Scale

The relationship between the BAI total score and the subscales of the BAI and the BDI, SCOPA-AUT and UPDRS-III were influenced by confounders, as mentioned in the addendum of Supplementary Table S1. The confounding variables were age and the BDI, SCOPA-AUT and UPDRS-III score. Although, as demonstrated in Table 2, these variables were all significantly correlated with each other, VIF remained within acceptable bounds.

Discussion

In this study, clinically relevant symptoms of anxiety were present in 45% of patients in our sample, which corresponds with previously reported rates (1, 2). PCA of the BAI revealed one affective and four somatic symptom dimensions (*thermoregulation, hypotension, hyperventilation* and *trembling*) of anxiety. The finding of a distinct affective factor and multiple somatic factors is in line with previous research on dimensionality of the BAI in non-PD samples (11, 13, 18, 19). In these studies, less than five factors were found, probably because the samples consisted of psychiatric patients with a mean age under 40 years. These patients are less likely to experience somatic symptoms than the patients in our sample, who have a variety of PD-related motor and non-motor symptoms that overlap with somatic anxiety equivalents. Moreover, differences in the methodology of the factor analysis, such as the choice of rotation method, can lead to a different number of obtained factors

The BDI significantly influenced all subscales of the BAI, as well as the BAI total score. Moreover, there was a high correlation between the BAI and BDI. This suggests that the large overlap between anxiety and depression that is found in psychiatric patients (20), is present in PD patients as well. In previous studies, anxiety and depressive disorders coexisted in 19 to 40% of patients with PD, which is higher than in matched controls (21-23).

Autonomic symptoms significantly influenced the total score on the BAI and on the *hypotension, thermoregulation* and *hyperventilation* subscales, while severity of motor symptoms influenced the score on the *trembling* subscale. The most obvious explanation for these observations is that the BAI is designed to measure episodic anxiety, such as in panic disorder, which is accompanied by somatic equivalents of anxiety (19). Alternatively, symptoms of PD-related autonomic and motor dysfunction might be misinterpreted as anxiety, resulting in overdiagnosis of anxiety disorders in PD patients (24). In this study, we demonstrated that the score on the *affect* subscale was not influenced by the SCOPA-AUT or the UPDRS-III score. One might therefore conclude that the *affect* subscale constitutes the most reliable measure of anxiety in PD, because it is not affected by 'noise' generated by motor and autonomic symptoms. The use of questionnaires excluding somatic symptoms for the screening of psychiatric disorders in the elderly has been advocated for this reason

(25). In PD patients, however, attempts to make a clear distinction between autonomic symptoms caused by anxiety and PD-related autonomic dysfunction will probably prove futile. The diagnostic criteria for anxiety disorders underline that physical symptoms comprise an integral part of the syndrome 'anxiety' (26). Moreover, PD-related autonomic symptoms and anxiety frequently co-occur and overlap in symptomatology (2, 24), and there is an interplay between anxiety and somatic symptoms (2, 3, 24). The development of autonomic failure in PD may lead to a pathophysiological predisposition towards somatic symptoms of anxiety. This hypothesis is supported by research in non-PD patients suffering from autonomic failure. For example, in patients with pure autonomic failure, hyperventilation causes a larger decrease in blood pressure than in healthy controls (27, 28). In a case-report on a patient with pure autonomic failure who experienced dizziness during emotional stress, a significant decrease in blood pressure after stressful events was demonstrated (29). Moreover, PD patients with failure of both the sympathetic and parasympathetic nervous system had higher levels of anxiety and depression than healthy controls or de novo PD patients (30). One may therefore expect that the presence of autonomic failure in PD patients gives rise to a stronger physical response to anxiety. The presence of anxiety is also associated with an increase in motor symptoms in PD (6-8). Vice versa, PD-related motor symptoms, such as wearing-off, can give rise to anxiety: a substantial number of PD patients suffers from situational anxiety, with phobic avoidance related to fear of experiencing off-periods or freezing (3). The clinical finding that many PD patients with response fluctuations experience anxiety and autonomic symptoms during wearing-off (6, 31, 32), suggests that dopaminergic transmission is involved in the etiology of both motor and non-motor symptoms of PD (33, 34). These findings make the distinction between anxiety and other motor and non-motor symptoms of PD appears artificial. In line with this, the MDS task force on rating scales for PD recommends an "inclusive approach" when rating possible symptoms of anxiety in PD patients, without trying to attribute them to either anxiety or other PD-related symptoms (35). The finding of an *affect* subscale of the BAI, that is not influenced by motor or autonomic symptoms, might nevertheless be relevant for research purposes. Moreover, our results can be useful in the development of new measures for anxiety in PD.

This study has some limitations. The only measure of anxiety in this study was the BAI. The BAI can be used to assess symptoms of anxiety, but is not a diagnostic instrument. Moreover, the BAI is more suitable for measuring episodic anxiety than the non-episodic anxiety that occurs in generalized anxiety disorder (18), which is one of the most prevalent anxiety disorders in PD patients (2). Strengths of the present study are the large number of patients included, and the homogeneity of the sample. Moreover, this is the first study that has successfully performed a factor analysis of the BAI in a sample of PD patients.

Conclusions

In this study, we demonstrated that anxiety in PD patients, as measured with the BAI, comprises one affective and four somatic symptom dimensions. Scores on the BAI and BDI are highly correlated, which can be explained by symptom overlap and frequent co-occurrence of anxiety and depression in PD.

The score on the somatic subscales of the BAI is significantly influenced by autonomic failure and motor dysfunction, whereas the *affect* subscale is not. This finding suggests that the *affect* subscale may be a more reliable measure of anxiety in PD patients. However, somatic symptoms cannot be completely disregarded in the diagnostic process of anxiety disorders. Furthermore, anxiety, autonomic failure and motor dysfunction in PD may share underlying etiological mechanisms. The strong interplay between motor and non-motor symptoms in PD warrants a holistic approach to anxiety in clinical practice. Hopefully, the findings in this study will stimulate the development of new and more specific measures of anxiety in PD.

Supplementary material

Figure S1: **Scree plot of the principal component analysis of the BAI.**

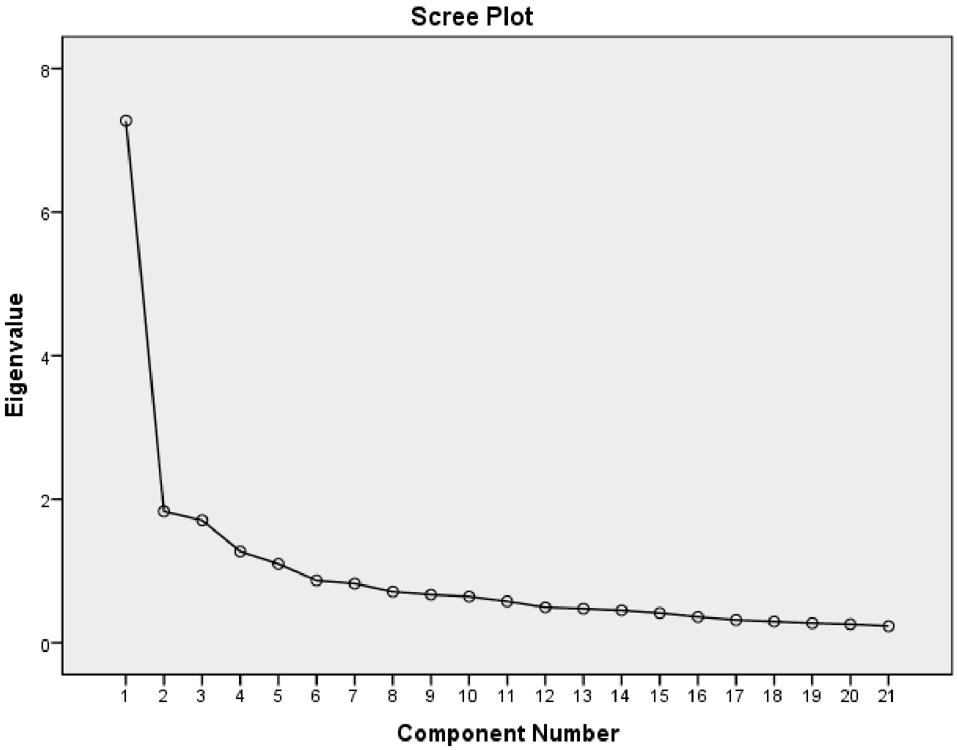

Table S1: **Results of multiple linear regression analysis association BAI total score and score on subscales of the BAI with BDI, SCOPA-AUT and UPDRS-III. All associations are adjusted for covariates in three consecutive models. Regression coefficients (B) and 95% confidence intervals (95%-CI) and significance (p-values, indicated with *) are displayed, as well as information on confounding covariates (Ad 1 – 11).**

		Crude model		Model 1		Model 2		Model 3	
		B	95%-CI	B	95%-BI	B	95%-CI	B	95%-CI
BAI total score									
BDI	1	0.904***	0.807 - 1.001	0.895***	0.797 - 0.992	0.895***	0.794 - 0.997	0.688***	0.582 - 0.794
SCOPA-AUT	2	0.695***	0.592 - 0.799	0.723***	0.617 - 0.829	0.730***	0.618 - 0.843	0.397***	0.294 - 0.501
UPDRS-III		0.187***	0.096 - 0.277	0.193***	0.099 - 0.288	0.173***	0.079 - 0.268	0.026	-.037 - 0.089
Subscale Affective									
BDI		0.381***	0.335 - 0.428	0.381***	0.335 - 0.428	0.394***	0.346 - 0.442	0.373***	0.318 - 0.428
SCOPA-AUT		0.199***	0.145 - 0.254	0.212***	0.156 - 0.268	0.219***	0.159 - 0.278	0.046	-.008 - 0.100
UPDRS-III		0.042*	0.001 - 0.083	0.047*	0.004 - 0.090	0.042	-.001 - 0.086	-.010	-.043 - 0.022
Subscale Thermoregulation									
BDI	3	0.102***	0.075 - 0.130	0.105***	0.078 - 0.133	0.098***	0.069 - 0.126	0.050**	0.020 - 0.080
SCOPA-AUT	4	0.107***	0.082 - 0.132	0.124***	0.100 - 0.149	0.120***	0.094 - 0.146	0.098***	0.069 - 0.128
UPDRS-III		0.0128	-.007 - 0.032	0.022*	0.002 - 0.042	0.017	-.003 - 0.037	-.005	-.023 - 0.013
Subscale Trembling									
BDI	5	0.075***	0.050 - 0.099	0.069***	0.045 - 0.093	0.076***	0.051 - 0.100	0.056***	0.029 - 0.084
SCOPA-AUT		0.060***	0.038 - 0.083	0.051***	0.028 - 0.074	0.059***	0.035 - 0.084	0.024	-.003 - 0.051
UPDRS-III	6	0.042***	0.026 - 0.058	0.036***	0.020 - 0.053	0.038***	0.021 - 0.055	0.027***	0.011 - 0.044
Subscale Hyperventilation									
BDI	7	0.045***	0.033 - 0.058	0.045***	0.033 - 0.058	0.042***	0.029 - 0.055	0.022**	0.008 - 0.036
SCOPA-AUT	8	0.050***	0.039 - 0.061	0.052***	0.041 - 0.064	0.050***	0.038 - 0.062	0.040***	0.026 - 0.054
UPDRS-III		0.011*	0.002 - 0.020	0.010*	0.001 - 0.019	0.008	-.001 - 0.017	-.001	-.010 - 0.007

Table S1, continued

Subscale Hypotension									
BDI	9	0.184***	0.155 - 0.214	0.179***	0.150 - 0.209	0.174***	0.143 - 0.205	0.105***	0.074 - 0.136
SCOPA-AUT	10	0.182***	0.156 - 0.208	0.183***	0.157 - 0.210	0.183***	0.154 - 0.211	0127***	0.096 - 0.157
UPDRS-III	11	0.060***	0.037 - 0.083	0.058***	0.034 - 0.081	0.052***	0.029 - 0.076	0.019*	0.001 - 0.038

* p-value <0.05, ** p-value < 0.01, *** p-value < 0.001

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory, SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; UPDRS = Unified Parkinson's disease Rating Scale

Model 1: adjustment for age and gender
Model 2: adjustment for age, gender, and use of dopaminergic medication
Model 3: adjustment for age, gender, use of dopaminergic medication, and score on the BDI and/or SCOPA and/or UPDRS-III score

Ad 1: confounding by the SCOPA-AUT score.
Ad 2: confounding by the UPDRS-III score.
Ad 3: confounding by the SCOPA-AUT score.
Ad 4: confounding by BDI score and age.
Ad 5: confounding by SCOPA-AUT score.
Ad 6: confounding by the SCOPA-AUT and BDI score and age.

Ad 7: confounding by the SCOPA-AUT score.
Ad 8: confounding by the BDI score.
Ad 9: confounding by the SCOPA-AUT score.
Ad 10: confounding by the BDI score.
Ad 11: confounding by the SCOPA-AUT en BDI score.

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3

Chapter 3

Predictors of anxiety in early-stage Parkinson's disease: results from the first two years of a prospective cohort study

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Abstract

Aim
Anxiety has a negative impact on daily functioning and quality of life in patients with Parkinson's disease (PD). This study aims at assessing which sociodemographic and clinical characteristics predict the course of anxiety in early PD.

Methods
The participants of this two-year prospective cohort study were recently diagnosed PD patients not receiving psychiatric medications or dopamine replacement therapy at baseline. Assessments were performed annually after baseline. The primary outcome measure was anxiety, as measured with the State-Trait Anxiety Inventory (STAI). Covariates were age, gender, family history, striatal dopamine transporter binding ratios, and severity of motor and non-motor features of PD at baseline. Data were analyzed using a mixed model analysis.

Results
Inclusion criteria were met by 306 subjects. An increase in STAI total score was predicted by older age, lower score on the Montreal Cognitive Assessment, and the presence of a probable REM-sleep behavior disorder (RBD) at baseline. A decrease in STAI total score over time was predicted by a higher baseline score on the 15-item Geriatric Depression Scale, compulsive behavior at baseline and a family history of PD.

Conclusions
More severe baseline anxiety was associated with compulsive behavior and depressive symptoms. These symptoms had a parallel course, showing a decrease over time. An increase in anxiety was predicted by older age, worse cognitive functioning and the presence of RBD. Our findings, when replicated in a sample of PD patients in a more advanced disease stage, could provide starting points for prevention of anxiety in PD patients.

Introduction

About 25% of PD patients experience clinically relevant symptoms of anxiety, and approximately one-third suffers from an anxiety disorder as specified by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (1). Anxiety frequently predates the development of motor symptoms in PD, and might be considered as one of the earliest manifestations of PD. Once motor symptoms develop, anxiety remains more frequent in PD patients than in controls (2). It can be socially disruptive, constitutes a source of disability (3), and has a negative impact on health-related quality of life (4). However, in neurological practice, anxiety is often under-recognized (5), and anxiety in PD has received little scientific attention.

The pathophysiology of anxiety in PD patients still has to be elucidated. Previous research suggests that anxiety in PD results from an interplay of psychological, social and neurobiological factors. Anxiety in PD may be partially explained as a psychological reaction to the development of disabling motor and non-motor symptoms. In addition, there is increasing evidence that anxiety disorders are directly related to the neurochemical changes in PD. Patients with response fluctuations may report anxiety when the effect of dopaminergic medication wears off (6), and some studies demonstrate a positive effect of dopaminergic treatment on anxiety (e.g., Stacy et al. (2010)) (7). These clinical findings suggest that the dopaminergic system is involved not only in the etiology of motor symptoms, but also in the development of anxiety. Dopamine transporter (DAT) single-photon emission computed tomography (SPECT) studies demonstrate a negative correlation between striatal DAT availability and symptoms of anxiety and depression in PD patients (8, 9). Besides the dopaminergic system, the noradrenergic and serotonergic systems are thought to be involved in the neurobiology of anxiety in PD, as well (9).

A better knowledge of risk factors for anxiety in PD might provide new starting points for both fundamental research on the pathophysiology of anxiety in PD, and for clinical studies on screening, prevention and treatment. In previous studies, anxiety in PD patients was associated with female sex, a history of anxiety disorders, a current depressive or impulse-control disorder, the severity of motor symptoms, striatal dopamine transporter (DAT) availability and autonomic failure (4, 6, 8, 10-12). An important limitation of most previous research on risk factors for anxiety in PD is the cross-sectional nature of the design. One longitudinal study on the course of neuropsychiatric symptoms has been performed (13), but this study only focused on the initiation of dopamine replacement therapy (DRT) as a risk factor for anxiety. The current study therefore aims at assessing which factors predict the course of anxiety in patients with early-stage PD, with a primary focus on clinical and sociodemographic predictors, and an assessment of striatal dopamine DAT availability.

Methods

Study design

For this study, we used data from the Parkinson's Progression Markers Initiative (PPMI), an ongoing multi-center cohort study designed to identify PD progression biomarkers (14). Follow-up assessments took place one (T1) and two years (T2) after baseline assessment (T0). The study received ethical approval from the institutional board at each site. For a complete overview of study procedures we refer to Marek et al. (2011) (14). We used data that were collected between June 2010 and November 2014.

Study population

Subjects with a recent diagnosis of idiopathic PD were eligible for inclusion. None of the subjects had yet started DRT at T0. All subjects provided written informed consent. We used the screening criteria for the PPMI study, as stated in the study protocol on the PPMI website (http://www.ppmi-info.org). In order to obtain proper assessments of the outcome measure and covariates of this sub-study, we also excluded subjects aged under 30 years at PD onset and subjects with a bipolar disorder, psychotic disorder or current substance abuse. Since psychiatric medications, especially antidepressants and anxiolytic/hypnotic medications can decrease the severity of anxiety symptoms and stabilize the affective status, we also excluded subjects that were using these medications already at baseline. The start of psychiatric medications during follow-up was allowed. We assessed the effect of the start of antidepressants and anxiolytic/hypnotic medications during follow-up on the association between anxiety and the predictors with a *post hoc* analysis.

Outcome and covariates

The primary outcome measure of this study was the total score on the State-Trait Anxiety Inventory (STAI) (15), measured at T0, T1 and T2. The STAI has a high validity and acceptable internal consistency and test-retest reliability in non-PD samples (16). While the STAI has not been validated in a sample of PD patients, the Movement Disorders Society task force on rating scales for PD suggests that it is a suitable outcome in PD subjects, based on experience with the STAI in previous studies in PD populations (17). The inventory comprises two subscales: a State and Trait subscale. The STAI has not been validated as an outcome measure in longitudinal studies. However, the State subscale was designed to measure a temporary state of anxiety, while the Trait subscale measures a more enduring pattern of anxiety. The combined STAI total score is therefore expected to be sensitive to

change. Clinically relevant anxiety is commonly defined as a STAI State score of ≥ 39 (18). For secondary research outcomes, we used the scores on the State and Trait subscales.
Age, sex, a self-reported family history of PD, and the severity of PD symptoms at baseline were included as covariates in the prediction model. The Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to assess motor and non-motor symptoms (19). Since item 1.4 inquires about an anxious mood, we omitted this item from the MDS-UPDRS part Ia and total score. Part IV covers motor complications and was not used in the analysis because these are uncommon in early, unmedicated PD. Other covariates were the total score on the Scales for Outcomes in Parkinson's disease – Autonomic (SCOPA-AUT), the Montreal Cognitive Assessment (MoCA), and the 15-item Geriatric Depression Scale (GDS-15) (20-22). Depression in PD is associated with the presence of a rapid eye movement (REM)-sleep behavior disorder (RBD) and excessive daytime sleepiness (EDS) (23, 24). Given the frequent co-occurrence of anxiety and depression in PD (25), RBD and EDS might also be markers for developing anxiety in PD. In this study, the presence of a probable RBD was defined as a score ≥6 on the REM-sleep Behavior Disorder Screening Questionnaire (RBDSQ) (26). The presence of a probable impulse control disorder (ICD) or compulsive behavior was determined with the cut-off scores on the abbreviated version of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) as described in the validation study by Weintraub et al. (27). Probable EDS was defined as a score ≥10 on the Epworth Sleepiness Scale (ESS) (28, 29).
Finally, we used the SPECT DAT binding ratios of the left and right caudate nucleus and putamen separately. For the procedures involving DAT scanning and calculation of binding ratios, we refer to the SPECT manual on the PPMI website.

Statistical analysis

Percentages or mean scores with standard deviations were calculated for demographics and clinical characteristics of the study population.
A linear mixed model analysis was used to determine which covariates at baseline predicted a change in STAI scores over the course of two years. Mixed models analysis is considered to be particularly suitable for analyzing longitudinal data. This technique has the advantage that it handles missing data by placing the data in long format, where the available data of each measurement are nested within persons. Therefore, imputation of missing values is not necessary.

The STAI total, State and Trait subscale score were the outcomes used in these analyses. For the selection of covariates with a significant contribution to the model, i.e. the predictors of anxiety, we used a stepwise forward selection procedure. Alpha was set at $p<0.10$, which is common in a selection procedure for a prediction model (30). We assessed whether the

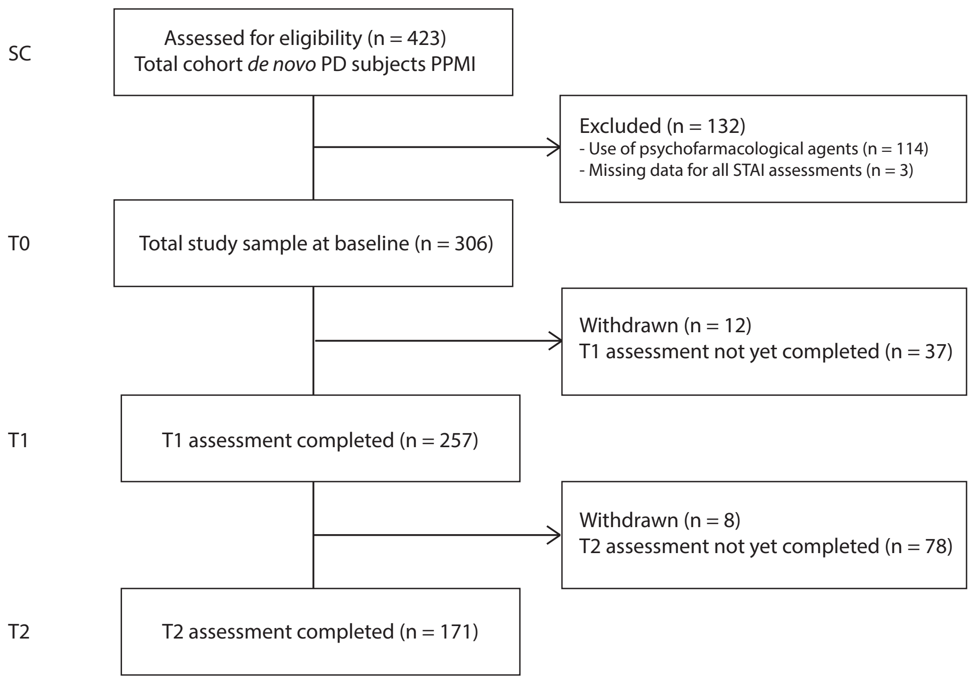
change in STAI scores over time was influenced by the baseline values of the covariates, by adding interaction terms with time (covariate by time) to the model. Random intercepts were included for study site and patient within study site. We calculated the regression coefficient with standard error (SE), Wald-statistic and 95% confidence interval for the interactions between covariate and time with a significant contribution to the regression model. Assumptions for mixed model analyses were checked.
For the mixed model analysis, we used MLwiN v2.32. All other analyses were performed with IBM SPSS Statistics 20.

Results

Subjects

At the time of analysis, PPMI had enrolled 423 subjects, of which 383 subjects completed the T1 and 229 subjects the T2 assessments. We excluded 114 subjects using psychiatric medications. Three additional subjects were excluded due to missing data for all three assessments of the STAI, resulting in a total sample size of 306 subjects. At the time of analysis, T1 assessment was completed by a total of 257 subjects, and T2 assessment by 171. A flow chart of this sub-study can be found in Figure 1.

Figure 1: **Flow chart**



As a sensitivity analysis, we compared the mean STAI total score for subjects that were included and excluded with an independent samples t-test. Subjects that were excluded had a higher mean STAI total score at baseline (72.5 vs. 62.9, $t = -4.30$, $df = 160.4$, $p < 0.001$), which was still significantly higher at T1 (69.1 vs. 63.6, $t = -2.56$, $df = 356.0$, $p < 0.05$), but not at T2 (68.4 vs. 63.8, $t = -4.68$, $df = 237.0$, $p = 0.06$).
Demographic and clinical characteristics of the study sample are presented in Table 1.

Table 1: **Demographic and clinical characteristics of the study population (n = 306).**

	%	Mean (SD)	Range
Female	32.0%		
Age (yrs)		61.5 (10.1)	34 - 84
Family history of PD	24.3%		
H&Y stage			
Stage I	46.1%		
Stage II	53.3%		
Stage III	0.7%		
MDS-UPDRS total $_{\text{adjusted*}}$		30.2 (12.5)	7 - 71
MDS-UPDRS part IA $_{\text{adjusted*}}$		0.7 (1.0)	0 - 5
MDS-UPDRS part IB		3.9 (2.9)	0 - 14
MDS-UPDRS part II		5.5 (4.0)	0 - 22
MDS UPDRS part III		20.1 (8.8)	4 - 51
SCOPA-AUT total score		8.9 (5.8)	0 - 39
MoCA total score		26.9 (2.4)	17 - 30
GDS-15 total score		2.0 (2.3)	0 - 14
RBDSQ total score		3.9 (2.6)	0 - 12
Probable RBD	22.9%		
QUIP total score		0.3 (0.8)	0 - 8
Probable ICD	9.2%		
Compulsive behavior	11.1%		
ESS total score		5.8 (3.4)	0 - 20
Probable EDS	15.7%		
DAT binding ratio			
right caudate nucleus		2.04 (0.59)	0.68 - 3.98
left caudate nucleus		2.03 (0.57)	0.57 - 3.72
right putamen		0.87 (0.35)	0.14 - 2.35
left putamen		0.82 (0.33)	0.27 - 2.32

*score on item 1.4 of the MDS-UPDRS was not included in the sum score

H&Y = Hoehn & Yahr; MDS-UPDRS = Movement Disorders Society - Unified Parkinson's Disease Rating Scale; SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; MoCA = Montreal Cognitive Assessment; GDS-15 = 15-item Geriatric Depression Scale; RBDSQ = REM-sleep behavior disorder Screening Questionnaire; RBD = REM-sleep behavior disorder; QUIP = Questionnaire for impulsive-compulsive disorders in Parkinson's disease; ICD = impulse control disorder; ESS = Epworth Sleepiness Scale; EDS = Excessive Daytime Sleepiness; DBR = DAT-binding ratio

Occurrence and course of anxiety

The mean STAI total score at baseline was 62.9 (SD ± 16.5) and, at group level, changed little over time. Across all visits, approximately 20% of subjects had clinically relevant symptoms of anxiety (see Supplementary Material).

Predictors of the course of anxiety

For an overview of the univariate analyses, we refer to the Supplementary material. Final models resulting from the multivariate mixed models analyses are presented in Table 2. To facilitate interpretation, the influence of the predictors on the STAI total scores are illustrated in Figure 2a – 2e. Note that in these figures, it is assumed that the values of all other predictors are zero.

Predictors of STAI total score

The first column of Table 2 displays details of the interactions between covariate and time with a significant contribution to the prediction model for the STAI total score. The value of the regression coefficient of the covariate indicates whether the association between the predictor at baseline and the STAI total score is positive or negative. The value of the regression coefficient of the interaction of the covariate with time indicates in which direction the association changes over time. E.g., for the subjects with compulsive behavior, there was a positive association with STAI total score at baseline, while the negative interaction with time ($p < 0.05$) indicates that the difference in mean STAI total score between the subjects with and without compulsive behavior decreased over time (and at some point might even reverse). The course of anxiety in these subgroups is demonstrated in Figure 2a.

A decrease in STAI total score over time was also predicted by a higher GDS-15 score at baseline ($p < 0.05$). In Figure 2b, subjects were divided into two groups based on the cut-off GDS-15 score ≥ 5, indicative of clinically relevant symptoms of depression (31). Subjects with clinically relevant symptoms of depression at baseline had a higher mean STAI total score at baseline that decreased over time, whereas the mean STAI total score in the subgroup without depression was lower at baseline and increased during follow-up. A positive family history of PD also predicted a decrease in STAI total score (see Figure 2c), but this association was less strong ($0.05 > p < 0.10$).

Table 2: **Results of the mixed models analysis of the STAI total, State and Trait subscale scores. Regression coefficients (B), standard error (SE), Wald-statistic and 95% confidence interval (95% CI) for the interaction terms of covariate X time that have a significant contribution to the model are printed in bold font.**

	STAI total score			STAI State score			STAI Trait score		
	B (SE)	Wald	95% CI	B (SE)	Wald	95% CI	B (SE)	Wald	95% CI
Compulsive behavior	*5.89 (2.51)*	*5.49*	*[0.96, 10.81]*	*5.13 (1.60)*	*10.28*	*[2.00, 8.27]*	*3.11 (1.31)*	*5.69*	*[0.55, 5.67]*
Compulsive behavior X Time	**-3.13 (1.47)**	**4.54**	**[-6.00, -0.25]**	**-2.10 (0.89)**	**5.64**	**[-3.84, -0.37]**	**-1.60 (0.75)**	**4.62**	**[-3.07, -0.14]**
Age	*-0.14 (0.08)*	*3.04*	*[-0.29, -0.02]*	-	-	-	*-0.11 (0.04)*	*7.33*	*[-0.19, -0.03]*
Age X time	**0.11 (0.05)**	**5.31**	**[0.02, 0.20]**	-	-	-	**0.07 (0.02)**	**7.34**	**[0.02, 0.11]**
Family history of PD	*0.31(1.82)*	*0.03*	*[-3.25, 3.87]*	*0.58 (1.15)*	*0.25*	*[-1.69, 2.83]*	-	-	-
Family history of PD X Time	**-2.03 (1.10)**	**3.67**	**[-4.10, 0.05]**	**-1.25 (0.64)**	**3.80**	**[-2.51, 0.01]**	-	-	-
Probable RBD	*0.86 (1.87)*	*0.21*	*[-2.81, 4.53]*	-	-	-	*0.32 (0.97)*	*0.11*	*[-1.58, 2.23]*
Probable RBD X time	**2.05 (1.09)**	**5.35**	**[0.38, 4.64]**	-	-	-	**1.19 (0.55)**	**4.72**	**[0.12, 2.26]**
GDS-15	*4.40(0.36)*	*148.22*	*[3.69, 5.10]*	-	-	-	*2.38 (0.19)*	*165.23*	*[2.02, 2.74]*
GDS-15 X time	**-0.42 (0.21)**	**4.06**	**[-0.82, -0.01]**	-	-	-	**-0.21 (0.11)**	**4.04**	**[-0.42, -0.01]**
MoCA	-	-	-	*-0.19 (0.20)*	*0.88*	*[-0.58, 0.21]*	-	-	-
MoCA X Time	-	-	-	**-0.25 (0.12)**	**4.65**	**[-0.47, -0.02]**	-	-	-

STAI = State-Trait Anxiety Inventory; RBD = REM-sleep behavior disorder; GDS-15 = 15-item Geriatric Depression Scale; MoCA = Montreal Cognitive Assessment

An increase in STAI total score over time was predicted by older age ($p < 0.05$) and the presence of probable RBD at baseline ($p < 0.05$). Figure 2d demonstrates that subjects with probable RBD had higher mean STAI scores at baseline, which increased over time, while the subjects without RBD had a lower mean STAI baseline score, which decreased further during follow-up. In the subgroups for age, divided using a median split for age, the mean STAI total scores at baseline differed little, and showed a fluctuating course over time (see Figure 2e).

Figure 2: **Course of the mean STAI total score over two years for different subgroups**

Figure 2a: **Mean STAI total score over the course of two years for subjects with and without compulsive behavior at baseline**

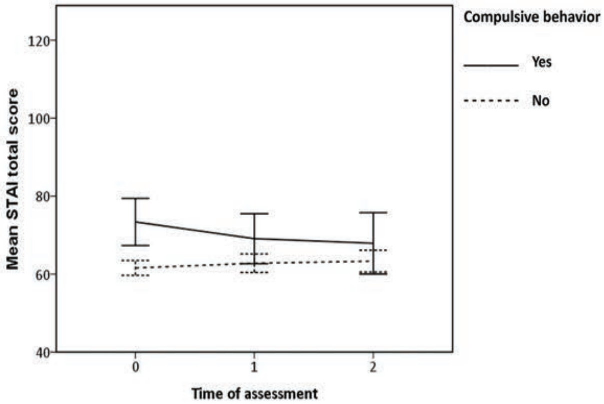


Figure 2b: **Mean STAI total score over the course of two years for subjects with and without a clinically relevant symptoms of depression**

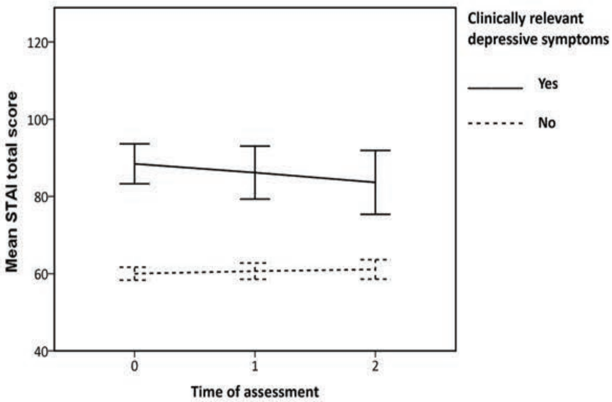


Figure 2, continued

Figure 2c: **Mean STAI total score over the course of two years for subjects with and without a self-reported familiy history of PD**

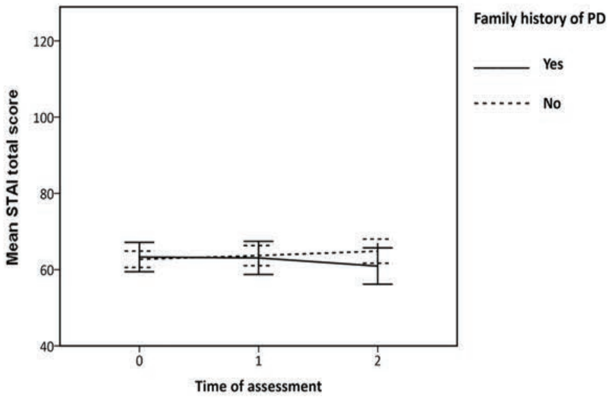


Figure 2d: **Mean STAI total score over the course of two years for subjects with and without a probable RBD**

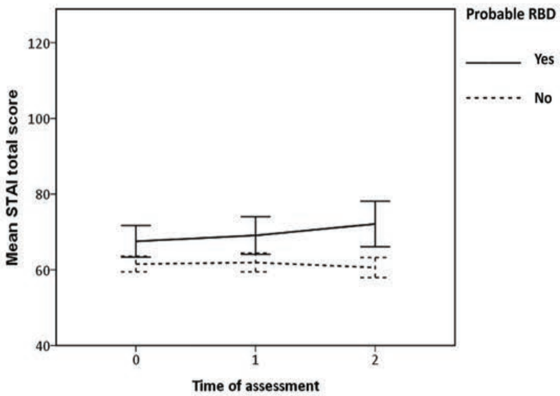
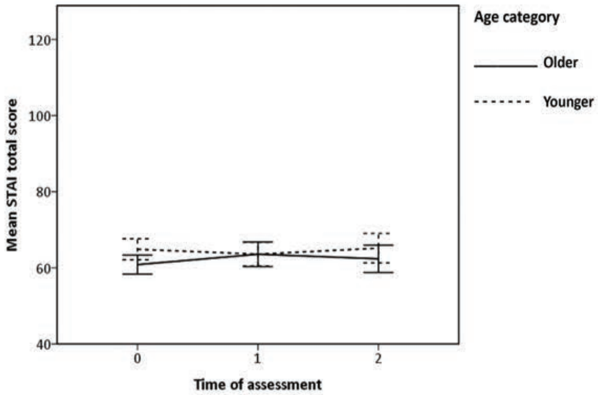


Figure 2e: **Mean STAI total score over the course of two years for older and younger subjects**



Predictors of STAI State and Trait subscale scores

Details of the interactions between covariate and time with a significant contribution to the prediction models for the STAI State and Trait score are displayed in Table 2. For an illustration of the course of the STAI subscale scores for these predictors, we refer to the Supplementary material.

A decrease in STAI State score over time was predicted by compulsive behavior at baseline ($p < 0.05$). The negative association between STAI State score and the interaction of a family history of PD with time was less strong ($0.05 > p < 0.10$). A lower baseline MoCA score predicted an increase in STAI State score ($p < 0.05$). Supplementary Figure S1c presents the differences between subjects with and without probable cognitive impairment, based on a MoCA cut-off score ≤ 26 (20). Subjects with probable cognitive impairment at baseline showed an increase in mean STAI State score over time, while the STAI State score remained stable in subjects without cognitive impairment.

A decrease in STAI Trait score was predicted by compulsive behavior ($p < 0.05$) and a higher GDS-15 score ($p < 0.05$) at baseline. An increase in STAI Trait score was predicted by older age ($p < 0.01$) and the presence of probable RBD ($p < 0.05$) at baseline.

As a *post hoc* analysis, we assessed the influence of the initiation of antiparkinsonian agents (DRT, amantadine or parasympaticolytics), antidepressants or anxiolytics on the prediction models of the STAI total, State and Trait scores. There was no confounding effect of these medications during follow-up.

Discussion

This is the first study to identify predictors of the course of symptoms of anxiety in early-stage PD patients. The longitudinal course of neuropsychiatric symptoms in PD was only studied previously by de la Riva et al. (2014), in the complete PPMI cohort, with a specific focus on the initiation of DRT as risk factor for anxiety (13). The start of DRT was not associated with new-onset anxiety, which is in line with the results of our *post hoc* analysis on the effect of DRT. Another *post hoc* analysis demonstrated that the start of antidepressants or anxiolytics also had no significant influence on the relation between the predictors and anxiety in our study population.

In a previous cross-sectional study, there was a positive association between higher anxiety scores and a younger age at PD onset (4). In our study, younger subjects also had higher anxiety scores at baseline compared to older subjects, but an older age predicted an increase in anxiety during follow-up. Of note, age had only a small effect on anxiety.

A decrease in STAI scores over time was predicted by higher GDS-15 baseline score, compulsive behavior at baseline, and a family history of PD. Since a family history of PD was not a strong predictor ($0.05 > p < 0.10$), we will not discuss this finding in detail. Our findings are in contrast with previous studies demonstrating that a history of mental illness is associated with a higher prevalence of anxiety disorders in PD (4, 6). Figures 2a and 2b suggest that these results are accounted for by the phenomenon of 'regression to the mean' (32). Subjects with compulsive behavior and a higher depression score also have higher levels of anxiety at baseline. Due to regression to the mean, subjects in the higher part of the distribution of STAI scores at baseline are less likely to have high STAI scores at follow-up assessments (32). An alternative explanation is that symptoms of anxiety, depression and compulsive behavior in our sample can be regarded at least partly as a reaction to the recent diagnosis of PD. The decrease in these symptoms might reflect a psychological adjustment over time. Unfortunately, subjects participating in PPMI were not asked whether they had started non-pharmacological treatment for symptoms of anxiety, such as psychotherapy. Therefore, we were unable to control for this factor.

Worse cognitive functioning at baseline was associated with an increase in STAI State score over time. This may be a reflection of the underlying neurodegenerative process: neuropathological research demonstrates involvement of the limbic system in PD subjects with MCI, which might explain co-occurrence of cognitive dysfunction and anxiety (33). Alternatively, it may be a psychological reaction to the experienced cognitive changes. Disturbances of executive functions, which constitute the core feature of neuropsychological deficits in PD patients, reduce the capacity to control cognitive, emotional and behavioral responses to challenging environmental situations (34). In clinical practice, PD patients report that they can get anxious when confronted with unexpected events, or when they feel flooded by an excess of stimuli. Moreover, the subjective experience of cognitive deterioration can elicit anticipatory anxiety for disease progression and future disability. In PD patients with early cognitive dysfunctions, improving executive control using cognitive rehabilitation strategies might increase the resilience to the development of anxiety. Moreover, future research on the effects of cholinesterase inhibitors should include the effect on symptoms of anxiety in PD patients with more severe cognitive dysfunctions.

Subjects with probable RBD had more symptoms of anxiety at baseline that increased over time, which is in line with a previous study (24). A potential explanation for this finding is a more diffuse neurodegenerative process in PD subjects with RBD, which is expressed in a different phenotype. Indeed, the presence of RBD in PD is associated with a higher risk of developing dementia, and more autonomic and psychiatric symptoms (35). Alternatively, the reduced quality of sleep caused by RBD leads to anxiety. Patients with PD and RBD display instability in the wake–sleep and non-REM–REM sleep transitions (36), that may result in a lower sleep quality. Sleep plays an important role in maintaining adaptive emotional regulation and reactivity (37) and sleep disturbances increase the risk of developing an anxiety disorder (38). Further research is necessary to assess whether pharmacological treatment of RBD in PD patients decreases or prevents symptoms of anxiety in this population.

In contrast to previous studies (8, 9), striatal DAT-binding ratio was not found to be significantly associated with anxiety. This is probably due to the fact that we investigated a study sample of patients that recently entered the symptomatic phase of PD, while the subjects in the abovementioned studies had a longer disease duration and therefore probably a more advanced stage of dopaminergic neurodegeneration.

This brings us to the limitations of our study. Throughout the study, STAI scores were relatively low and changed little over time. Approximately 20% of our subjects suffered from clinically relevant symptoms of anxiety, which is substantially lower than in other studies in PD patients (1). Although this may be partially explained by the use of different instruments to measure anxiety across studies, it is probably due to a selection bias. All subjects in our study are early-stage, medication-naïve PD patients, and we excluded subjects using psychiatric medications at baseline. Sensitivity analysis showed that the excluded subjects demonstrated higher mean STAI total scores during follow-up. With our in- and exclusion criteria, we thus selected a study sample that is presumably mentally healthier than the general PD population. This limits the generalizability of our results. Conversely, the exclusion of subjects taking psychiatric medications or dopaminergic agents at baseline, ensured that there was no influence of these pharmacological agents on the assessment of anxiety at, or shortly after, baseline assessment. Moreover, our study sample comprised PD patients in an early stage of their disease. These characteristics of our study sample are unique compared to other studies on anxiety in PD.

As follow-up of the PPMI cohort continues, we expect to find larger changes in both motor and non-motor symptoms within subjects. Therefore, it will be informative to repeat this study when the subjects in the PPMI cohort have progressed to a more severe disease stage. We did, however, identify potential risk factors for anxiety in PD that warrant future research and might be relevant for clinical practice. Of note, we realize that the clinical relevance of the observed changes in STAI scores is questionable, and therefore we want to emphasize that we present the implications of our findings for clinical practice with reserve.

In conclusion, we found that the course of anxiety over two years in a sample of early-stage PD patients was predicted by age, cognitive functioning, the severity of depressive symptoms, and the presence of a RBD and compulsive behavior at baseline. These findings may provide new starting points for research on the pathophysiology, prevention and treatment of anxiety disorders in PD.

Supplementary material

Table S1: **Overview of anxiety measures at baseline (T0), after one year (T1) and two years (T2) of follow-up.**

	T0 (n = 306)		T1 (n = 257)		T2 (n = 171)	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
STAI total score	62.9 (16.5)	40 - 120	63.6 (18.1)	40 - 117	63.8 (17.3)	40 - 132
STAI State score	31.7 (9.1)	20 - 60	31.7 (9.6)	20 - 63	31.8 (9.4)	20 - 66
STAI Trait score	31.2 (8.8)	20 - 63	31.8 (9.4)	20 - 60	32.0 (9.2)	20 - 66
Clinically relevant symptoms of anxiety*	22.7%		22.9%		21.4%	

* Defined as a STAI State score of ≥ 39.

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Table S2: **Univariate analyses for scores on the STAI total, State and Trait subscale, displaying regression coefficients (B), standard errors (SE), Wald-statistic and 95% confidence interval (95% CI).**

	STAI total score			STAI State score			STAI Trait score		
	B (SE)	**Wald**	**95% CI**	**B (SE)**	**Wald**	**95% CI**	**B (SE)**	**Wald**	**95% CI**
Constant	63.65 (1.71)	1388.65	[60.30, 67.00]	31.67 (0.93)	1171.93	[29.85, 33.48]	32.11 (0.90)	1269.92	[30.34, 33.87]
Time	-0.63 (0.85)	0.56	[-2.29, 1.03]	-0.02 (0.50)	0.00	[-1.01, 0.97]	-0.51 (0.43)	1.39	[-1.35, 0.34]
Gender	-0.84 (2.04)	0.17	[-4.83, 3.15]	0.09 (1.11)	0.01	[-2.08, 2.25]	-1.10 (1.08)	1.03	[-3.21, 1.02]
Gender X time	1.11 (1.02)	1.16	[-0.90, 3.11]	-0.02 (0.61)	0.00	[-1.22, 1.18]	1.01 (0.52)	3.74	[-0.01, 2.03]
Constant	74.40 (5.84)	162.57	[62.96, 85.83]	34.79 (3.17)	120.65	[28.58, 40.99]	39.69 (3.08)	165.62	[33.64, 45.73]
Time	-6.96 (2.92)	5.71	[-12.69, -1.26]	-3.01 (1.75)	2.95	[-6.45, 0.42]	-4.09 (1.49)	7.56	[-7.01, -1.18]
Age	-0.19 (0.09)	3.87	[-0.37, -0.01]	-0.05 (0.05)	0.96	[-0.15, 0.05]	-0.14 (0.05)	7.40	[-0.23, -0.04]
Age X time	0.12 (0.05)	5.99	[0.023, 0.21]	0.05 (0.03)	2.94	[-0.01, 0.10]	0.07 (0.02)	8.27	[0.02, 0.12]
Constant	85.84 (1.14)	3030.88	[60.58, 65.05]	31.58 (0.62)	2636.45	[30.37, 32.78]	31.28 (0.60)	2718.06	[30.11, 32.46]
Time	-1.26 (0.56)	1.49	[-0.41, 1.77]	0.31 (0.33)	0.84	[-0.35, 0.96]	0.42 (0.29)	2.19	[-0.14, 0.98]
Family history PD	-0.00 (2.16)	0.16	[-3.38, 5.09]	0.50 (1.18)	0.18	[-1.81, 2.80]	0.23 (1.15)	0.04	[-2.03, 2.48]
Family history PD X time	0.21 (1.08)	3.45	[-4.14, 0.11]	-1.24 (0.65)	3.70	[-2.50, 0.02]	-0.86 (0.56)	2.38	[-1.94, 0.23]
Constant	59.28 (1.15)	2643.19	[57.02, 61.54]	30.10 (0.63)	2261.43	[28.86, 31.34]	29.19 (0.60)	2397.88	[28.02, 30.35]
Time	0.54 (0.59)	0.83	[-0.62, 1.70]	0.10 (0.35)	0.08	[-0.59, 0.79]	0.34 (0.30)	1.25	[-0.25, 0.93]
UPDRS Ia	5.55 (0.93)	35.59	[3.73, 7.37]	2.38 (0.51)	21.61	[1.38, 3.38]	3.18 (0.49)	42.76	[2.23, 4.13]
UPDRS Ia X time	-0.63 (0.49)	1.67	[-1.59, 0.33]	-0.22 (0.28)	0.63	[-0.77, 0.33]	-0.25 (0.25)	0.96	[-0.74, 0.25]
Constant	57.10 (1.61)	1258.00	[53.95, 63.40]	29.41 (0.88)	1111.87	[27.68, 31.14]	27.67 (0.84)	1084.84	[26.02, 29.31]
Time	-0.26 (0.83)	0.10	[-1.88, 0.63]	-0.63 (0.49)	1.65	[-1.59, 0.33]	0.44 (0.42)	1.10	[-0.38, 1.27]
UPDRS Ib	1.51 (0.33)	21.28	[0.87, -41.38]	0.59 (0.18)	10.63	[0.23, 0.94]	0.94 (0.17)	29.80	[0.60, 1.28]
UPDRS Ib X time	0.10 (0.17)	0.35	[-0.23, -0.51]	0.15 (0.10)	2.25	[-0.05, 0.35]	-0.07 (0.09)	0.56	[-0.24, 0.11]

Table S2, continued

	STAI total score			STAI State score			STAI Trait score		
	B (SE)	**Wald**	**95% CI**	**B (SE)**	**Wald**	**95% CI**	**B (SE)**	**Wald**	**95% CI**
Constant	60.23 (1.61)	1392.76	[57.07, 63.40]	30.47 (0.88)	1206.71	[28.75, 32.18]	29.73 (0.85)	1217.37	[28.06, 31.40]
Time	-0.90 (0.82)	1.20	[-2.50, 0.71]	-0.68 (0.49)	1.96	[-1.63, 0.27]	-0.13 (0.42)	0.09	[-0.95, 0.70]
UPDRS II	0.51 (0.23)	4.96	[0.06, 0.96]	0.23 (0.13)	3.25	[-0.02, 0.47]	0.30 (0.12)	5.85	[0.06, 0.53]
UPDRS II X time	0.18 (0.12)	2.29	[-0.05, 0.41]	0.12 (0.07)	2.62	[-0.02, 0.25]	0.05 (0.06)	0.78	[-0.07, 0.17]
Constant	61.80 (2.27)	740.53	[57.35, 66.25]	31.42 (1.24)	639.78	[28.98, 33.85]	30.34 (1.21)	624.59	[27.96, 32.72]
Time	-1.10 (1.23)	0.81	[-3.51, 1.30]	-0.95 (0.73)	1.69	[-2.39, 0.48]	-0.05 (0.63)	0.01	[-1.28, 1.19]
UPDRS III	0.06 (0.10)	0.39	[-0.14, 0.26]	0.02 (0.06)	0.08	[-0.09, 0.13]	0.05 (0.06)	0.86	[-0.06, 0.16]
UPDRS III X time	0.06 (0.06)	1.15	[-0.05, 0.17]	0.05 (0.03)	1.86	[-0.02, 0.11]	0.01 (0.03)	0.15	[-0.04, 0.07]
Constant	57.51 (2.41)	569.01	[52.79, 62.24]	29.61 (1.32)	506.08	[27.03, 32.18]	27.76 (1.28)	470.48	[25.26, 30.27]
Time	-1.44 (1.29)	1.25	[-3.95, 1.08]	-1.32 (0.77)	2.95	[-2.81, 0.18]	-0.02 (0.66)	0.00	[-1.31, 1.27]
UPDRS total	0.19 (0.07)	6.42	[0.04, 0.33]	0.07 (0.04)	3.15	[-0.01, 0.15]	0.12 (0.04)	9.31	[0.04, 0.20]
UPDRS total X time	0.05 (0.04)	1.64	[-0.03, 0.13]	0.04 (0.02)	3.33	[0.00, 0.09]	0.01 (0.02)	0.09	[-0.03, 0.05]
Constant	57.03 (1.76)	1047.75	[53.58, 60.49]	28.79 (0.96)	903.39	[26.92, 30.67]	28.20 (0.93)	919.65	[26.38, 30.03]
Time	-0.39 (0.88)	0.19	[-2.11, 1.34]	-0.33 (0.53)	0.38	[-1.36, 0.71]	-0.05 (0.45)	0.01	[-0.93, 0.83]
SCOPA-AUT	0.66 (0.16)	16.49	[0.34, 0.98]	0.32 (0.09)	13.09	[0.15, 0.50]	0.35 (0.09)	16.19	[0.18, 0.51]
SCOPA-AUT X time	0.04 (0.08)	0.27	[-0.12, 0.20]	0.02 (0.05)	0.18	[-0.08, 0.12]	0.02 (0.04)	0.29	[-0.06, 0.10]
Constant	75.24 (10.15)	54.96	[55.34, 95.13]	37.45 (5.51)	46.25	[26.65, 48.24]	38.23 (5.46)	49.07	[27.53, 48.92]
Time	9.07 (5.17)	3.08	[-1.06, 19.20]	6.25 (3.08)	4.11	[0.20, 12.29]	2.44 (2.65)	0.85	[-2.75, 7.63]
MoCA	-0.45 (0.38)	1.44	[-1.19, 0.29]	-0.21 (0.20)	1.08	[-0.61, 0.19]	-0.25 (0.20)	1.58	[-0.65, 0.14]
MoCA X time	-0.34 (0.19)	3.04	[-0.71, 0.04]	-0.24 (0.12)	4.18	[-0.46, -0.01]	-0.09 (0.10)	0.74	[-0.28, 0.11]

3

Table S2, continued

	STAI total score			STAI State score			STAI Trait score		
	B (SE)	**Wald**	**95% CI**	**B (SE)**	**Wald**	**95% CI**	**B (SE)**	**Wald**	**95% CI**
Constant	53.70 (1.11)	2344.78	[51.53, 55.87]	27.50 (0.64)	1863.47	[26.25, 28.75]	26.25 (0.57)	2127.82	[25.13, 27.36]
Time	1.04 (0.63)	2.70	[-0.20, 2.28]	0.34 (0.38)	0.81	[-0.40, 1.09]	0.69 (0.32)	4.52	[0.05, 1.32]
GDS-15	4.60 (0.36)	162.09	[3.89, 5.30]	2.08 (0.21)	100.58	[1.67, 2.48]	2.50 (0.19)	181.09	[2.14, 2.87]
GDS-15 X time	-0.46 (0.20)	5.12	[-0.85, -0.06]	-0.20 (0.12)	2.62	[-0.43, 0.04]	-0.25 (0.10)	5.75	[-0.45, -0.05]
Constant	62.15 (1.10)	3168.85	[59.98, 64.31]	31.18 (0.60)	2736.20	[30.01, 32.34]	30.93 (0.58)	2833.13	[29.79, 32.06]
Time	-0.39 (0.55)	0.49	[-1.47, 0.70]	-0.27 (0.33)	0.68	[-0.92, 0.38]	-0.09 (0.28)	0.10	[-0.65, 0.46]
Probable RBD	4.17 (2.20)	3.59	[-0.14, 8.47]	2.48 (1.19)	4.35	[0.15, 4.80]	1.94 (1.17)	2.74	[-0.36, 4.24]
Probable RBD X time	1.91 (1.09)	3.08	[-0.22, 4.04]	0.89 (0.65)	1.84	[-0.39, 2.16]	1.02 (0.56)	3.35	[-0.07, 2.11]
Constant	62.42 (1.04)	3588.61	[60.38, 64.46]	31.43 (0.56)	3116.14	[30.32, 32.53]	30.95 (0.55)	3225.61	[29.88, 32.02]
Time	0.19 (0.50)	0.14	[-0.79 1.17]	0.03 (0.30)	0.01	[-0.55, 0.61]	0.20 (0.26)	0.13	[-0.59, 0.41]
Probable ICD	7.28 (3.30)	4.86	[0.81, 13.75]	3.41 (1.79)	3.62	[-0.10, 6.92]	4.15 (1.74)	5.67	[0.74, 7.57]
Probable ICD X time	-0.52 (1.70)	0.09	[-3.85, 2.82]	-0.54 (1.02)	0.28	[-2.53, 1.46]	0.03 (0.87)	0.00	[-1.68, 1.73]
Constant	61.88 (1.05)	3465.97	[59.82, 63.93]	31.16 (0.57)	3009.91	[30.05, 32.28]	30.68 (0.55)	3099.52	[29.60, 31.76]
Time	0.57 (0.51)	1.28	[-0.42, 1.56]	0.18 (0.30)	0.36	[-0.41, 0.77]	0.43 (0.26)	2.75	[-0.08, 0.93]
Compulsive behavior	10.63 (2.98)	12.69	[4.78, 16.47]	5.05 (1.62)	9.76	[1.88, 8.22]	5.79 (1.58)	13.43	[2.69, 8.89]
Compulsive behavior X time	-3.78 (1.47)	6.58	[-6.66, -0.89]	-1.79 (0.89)	4.07	[-3.52, -0.05]	-2.05 (0.75)	7.47	[-3.52, -0.58]
Constant	6.78 (1.09)	39.61	[4.67, 8.89]	31.61 (0.58)	2959.10	[30.47, 32.74]	31.18 (0.57)	3034.73	[30.07, 32.29]
Time	-0.11 (0.52)	0.04	[-1.13, 0.91]	-0.16 (0.31)	0.27	[-0.77, 0.45]	0.08 (0.27)	0.10	[-0.44, 0.61]
Probable EDS	1.91 (2.48)	0.59	[-2.96, 6.77]	0.79 (1.36)	0.34	[-1.87, 3.45]	1.17 (1.33)	0.78	[-1.43, 3.78]
Probable EDS X time	1.50 (1.32)	1.29	[-1.09, 4.08]	0.85 (0.79)	1.15	[-0.70, 2.39]	0.63 (0.68)	0.86	[-0.70, 1.95]

Table S2, continued

	STAI total score			STAI State score			STAI Trait score		
	B (SE)	**Wald**	**95% CI**	**B (SE)**	**Wald**	**95% CI**	**B (SE)**	**Wald**	**95% CI**
Constant	62.79 (3.44)	333.34	[56.05, 69.53]	31.78 (1.87)	290.11	[28.13, 35.44]	31.19 (1.82)	292.48	[27.62, 34.77]
Time	2.21 (1.82)	1.48	[-1.35, 5.76]	1.40 (1.08)	1.68	[-0.72, 3.52]	0.86 (0.93)	0.85	[-0.97, 2.68]
DBR right caudate nucleus	0.14 (1.61)	0.01	[-3.01 3.29]	-0.03 (0.87)	0.00	[-1.74, 1.68]	0.08 (0.85)	0.01	[-1.59, 1.75]
DBR right caudate nucleus X time	-1.02 (0.86)	1.42	[-2.70, 0.66]	-0.70 (0.51)	1.89	[-1.70, 0.30]	-0.33 (0.44)	0.57	[-1.19, 0.53]
Constant	61.13 (3.46)	312.55	[54.36, 67.91]	30.64 (1.88)	265.60	[26.95, 34.32]	30.61 (1.83)	278.57	[27.02, 34.20]
Time	2.08 (1.77)	1.37	[-1.40, 5.54]	1.27 (1.06)	1.45	[-0.80, 3.34]	0.87 (0.91)	0.92	[-0.91, 2.64]
DBR left caudate nucleus	0.95 (1.62)	0.34	[-2.23, 4.13]	0.53 (0.88)	0.36	[-1.20, 2.26]	0.37 (0.86)	0.18	[-1.32, 2.06]
DBR left caudate nucleus X time	-0.96 (0.84)	1.31	[2.60, 0.68]	-0.64 (0.50)	1.65	[-1.62, 0.34]	-0.34 (0.43)	0.62	[-1.18, 0.50]
Constant	63.02 (2.47)	650.34	[58.17, 67.86]	31.61 (1.35)	550.02	[28.97, 34.26]	31.42 (1.32)	569.02	[28.83, 34.00]
Time	1.23 (1.33)	0.84	[-1.39, 3.84]	0.71 (0.80)	0.80	[-0.85, 2.27]	0.42 (0.68)	0.38	[-0.92, 1.76]
DBR right putamen	0.07 (2.59)	0.00	[-5.01, 5.16]	0.13 (1.42)	0.01	[-2.65, 2.91]	-0.06 (1.39)	0.00	[-2.78, 2.66]
DBR right putamen X time	-1.29 (1.45)	0.79	[-4.14, 1.56]	-0.87 (0.87)	1.01	[-2.57, 0.82]	-0.28 (0.75)	0.14	[-1.74, 1.18]
Constant	60.80 (2.51)	589.16	[55.89, 65.71]	30.41 (1.36)	496.99	[27.73, 33.08]	30.35 (1.33)	523.98	[27.75, 32.95]
Time	1.08 (1.29)	0.70	[-1.45, 3.60]	0.69 (0.77)	0.81	[-0.81, 2.20]	0.28 (0.66)	0.18	[-1.01, 1.57]
DBR left putamen	2.76 (2.79)	0.98	[-2.71, 8.23]	1.60 (1.52)	1.11	[-1.38, 4.59]	1.23 (1.48)	0.69	[-1.68, 4.13]
DBR left putamen X time	-1.17 (1.47)	0.63	[-4.04, 1.71]	-0.89 (0.88)	1.03	[-2.60, 0.83]	-0.12 (0.75)	0.02	[-1.59, 1.35]

MDS-UPDRS = Movement Disorders Society - Unified Parkinson's Disease Rating Scale; SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; MoCA = Montreal Cognitive Assessment; GDS-15 = 15-item Geriatric Depression Scale; RBD = REM-sleep behavior disorder; ICD = impulse control disorder; EDS = Excessive Daytime Sleepiness; DBR = DAT-binding ratio

3

Figure S1: **Course of the mean STAI State score over two years for different subgroups**

Figure S1a: **Mean STAI State score over the course of two years for subjects with and without compulsive behavior at baseline**

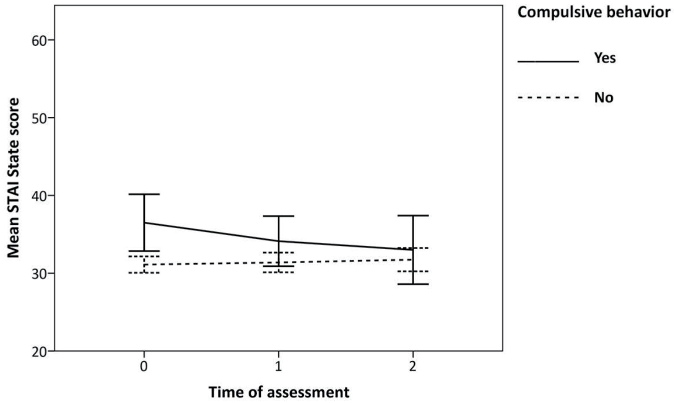


Figure S1b: **Mean STAI State score over the course of two years for subjects with and without a self-reported family history of PD**

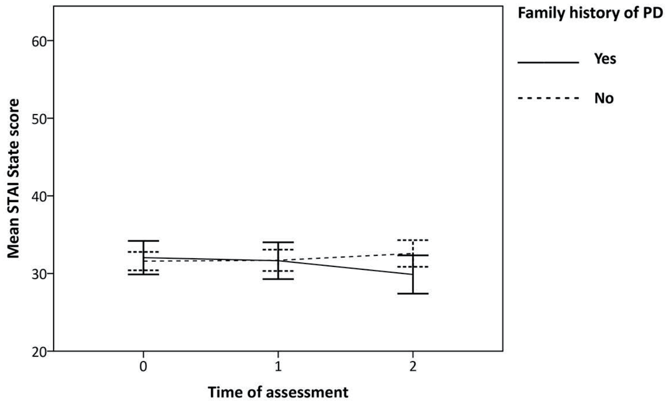


Figure S1c: **Mean STAI State score over the course of two years for subjects with and without probable cognitive impairment**

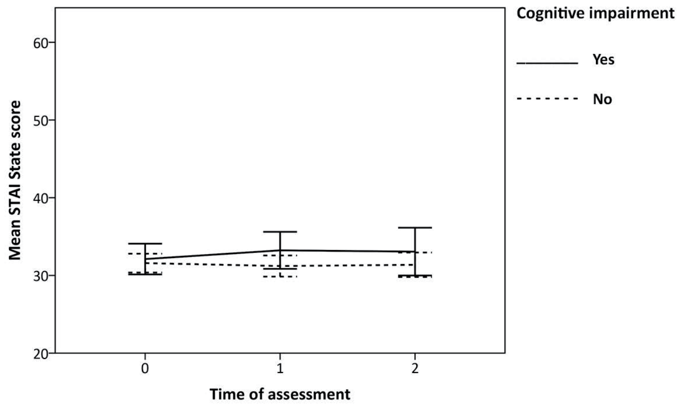


Figure S2: Course of the mean STAI Trait score over two years for different subgroups

Figure S2a: **Mean STAI Trait score over the course of two years for subjects with and without compulsive behavior at baseline**

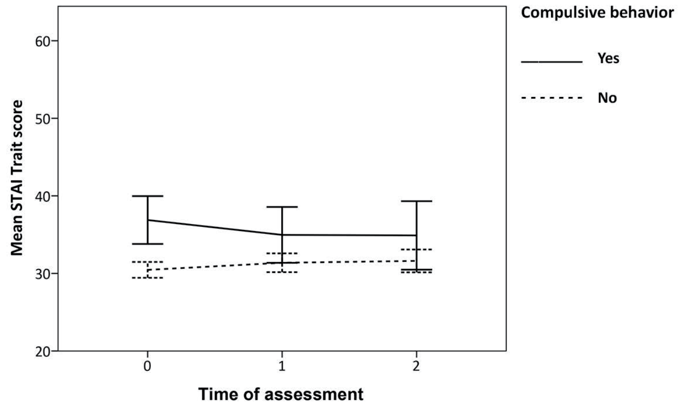
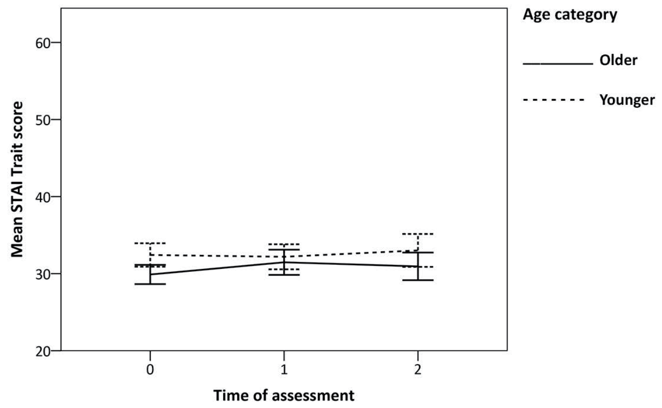


Figure S2b: **Mean STAI total score over the course of two years for older and younger subjects**



3

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4

Chapter 4

The bidirectional longitudinal relationship between insomnia, depression and anxiety in patients with early-stage, medication-naïve Parkinson's disease

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Abstract

Introduction

While anxiety, depression and insomnia frequently (co-)occur in Parkinson's disease (PD) patients, little is known about their temporal relationship. In this study, we tested two hypotheses: i) insomnia predicts an increase in symptoms of depression or anxiety and ii) anxiety or depression at baseline predicts insomnia in PD patients six months later.

Methods

We used longitudinal data from a prospective cohort study of early-stage, medication-naïve PD patients. Primary outcome measures were: anxiety symptoms, measured with the State-Trait Anxiety Inventory (STAI); depressive symptoms, measured with the 15-item Geriatric Depression Scale (GDS-15) and insomnia, defined as a score $\geq$ 2 on item 1.7 of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale. We performed linear and logistic regression analyses, correcting for baseline value of the respective outcome variable.

Results

Baseline insomnia was not associated with GDS-15 or STAI total score at follow-up. In a post hoc analysis, we found that insomnia predicted a higher STAI State score (B (SE) = 2.50 (1.07), $p < 0.05$), while the association with the STAI Trait score was not significant. Baseline STAI scores (B (SE) = 0.02 (0.01), $p = 0.001$) and GDS-15 score (B (SE) = 0.15 (0.05), $p < 0.001$) were significantly associated with insomnia at follow-up.

Conclusion

Symptoms of anxiety and depression may constitute a risk factor for insomnia in PD. The relationship between insomnia and anxiety is bidirectional, which suggests that both anxiety and sleep disorders can start a negative spiral in PD patients, where one enhances the other. Independent clinical attention for these symptoms in PD patients is therefore warranted.

Introduction

Parkinson's disease (PD) is accompanied by many non-motor symptoms, including sleep disorders, anxiety and depression. Anxiety and depression are associated with an increase of motor symptom severity and cognitive impairment and have a major negative impact on daily functioning (1-3). Clinically relevant symptoms of depression occur in 35% (6), and of anxiety in approximately 25% of PD patients (7). These prevalence rates are substantially higher than in age-matched controls or the general population (5, 8, 9). Co-occurrence of anxiety and depression is common, with a prevalence reported up to 40% (10). Insomnia, including complaints of an insufficient amount of sleep due to difficulties falling asleep, sleep fragmentation or early awakening, occurs in up to 40% of PD patients (4, 5).

Despite the frequent occurrence and negative impact of anxiety, depression and insomnia in PD patients, little is known about their course and interaction. In various cross-sectional studies, an association between insomnia and both depression and anxiety was found (5, 11-13). To our knowledge, however, no longitudinal study has examined the association between sleep disturbances and anxiety and depression in PD patients.

A better understanding of the temporal evolution of these symptoms might provide starting points for preventive strategies. Therefore, in this study, we analysed the relationship between insomnia and symptoms of depression and anxiety using data of an on-going prospective cohort study in early-stage, medication-naïve PD patients. We selected this study sample for two reasons. Firstly, clinical and research findings suggest that treatment with dopaminergic agents can affect sleep and mood in PD patients. Administration of levodopa suppresses REM sleep and lengthens REM sleep latency, while long-term treatment with dopamine agonists is associated with excessive daytime sleepiness and 'sleep attacks' in PD patients (19). Research and clinical findings also suggest that dopamine agonists may improve depressive symptoms (20). Selection of a study sample of medication-naïve PD patients thus enabled us to assess the association between sleep and mood in PD, without the interference of treatment with antiparkinsonian agents. Secondly, research on starting points for prevention of insomnia and anxiety and depressive disorders should be aimed at early-stage PD patients, since their prevalences increase with disease duration (4, 21).

In this study, we performed a bidirectional analysis of the relationship between insomnia and symptoms of depression and anxiety in PD patients, in order to test two hypotheses: i) insomnia at baseline predicts an increase in symptoms of depression and/or anxiety over time and ii) the severity of anxiety or depression at baseline predicts the subsequent occurrence of insomnia in PD patients.

Methods

Design and study procedures

We used data from the Parkinson's Progression Markers Initiative (PPMI) (10), an international, multicenter prospective cohort study that collects longitudinal data to assess disease progression in PD patients. The study received ethical approval from institutional boards of all 24 participating centers. Subjects participating in PPMI were recruited by their physician. All subjects provided written informed consent.
In the first year of participation in PPMI, assessments took place every three months. For this sub-study, we used the data that were collected at baseline (T0) and after approximately six months of follow-up (T1), since depression and anxiety measures were not assessed at the initial three-month follow-up visit.

Study population

The study population consisted of early-stage, medication-naïve PD patients. For details on the inclusion criteria, we refer to the study protocol on the PPMI website: www.ppmi-info.org. In some subjects, PD medication needed to be initiated within six months from baseline. In this case, the subject was asked to come in for an advanced assessment instead of the regular follow-up assessment, so a final PD medication-free assessment could be performed. We excluded subjects in whom antiparkinsonian agents were initiated within three months from baseline, or between three and six months from baseline without having a medication-free assessment before T1. Finally, we excluded subjects with missing data for any of the primary outcome measures at T1.

Sample size
PPMI finished enrolment of 423 subjects in April 2013. Six-month follow-up data was collected for 402 subjects. As a rule of thumb, the number of subjects needs to be ten times the number of covariates added to a prediction model. Since we added a maximum of 8 covariates to the prediction model (see section 'Outcome measures' below), we expected this sample size to be sufficiently powered.

Outcome measures

The primary outcome measures of our study were: anxiety, measured as the total score of the State-Trait Anxiety Inventory (STAI) (22), depressive symptoms, measured as the total score of the 15-item Geriatric Depression Scale (GDS-15) (23), and insomnia, defined as a score ≥ 2 on item 1.7 of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (24).

The STAI is a self-report questionnaire, which contains a "state" subscale, designed to measure a temporary state of anxiety, and a "trait" subscale that measures a more persistent pattern of anxiety (22). Clinically relevant anxiety in geriatric patients is defined as a STAI State score > 54 (25). The GDS-15 is a 15-item self-report questionnaire regarding depressive symptoms (25). In patients with PD, a score ≥ 5 is indicative of clinically relevant symptoms of depression (26). Insomnia was rated on item 1.7 of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (24). Item 1.7 is a single question: "Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning.". Although this is a one-item insomnia rating, it appears to be quite reliable (27). In this study, we considered a MDS-UPDRS 1.7 score ≥ 2, indicating mild to moderate sleep problems causing difficulties in getting a full night of sleep, to be suggestive of insomnia.

Statistical analyses

All analyses were performed with IBM SPSS Statistics 22 (Armonk, NY, USA). Demographics and clinical characteristics of the research population at baseline, and values of the outcome variables after approximately six months of follow-up, were summarized using percentages or mean scores with standard deviations. Correlations between continuous variables at baseline were calculated using Pearson's correlation coefficients.

We used a linear regression analysis to assess whether the presence of insomnia at baseline predicted the severity of depressive symptoms after six months of follow-up. We corrected for baseline severity of depression by adding the baseline GDS-15 score to the model. Finally, we examined whether sex, age, severity of motor symptoms (measured with the MDS-UPDRS section III score) (24), global cognitive function (assessed with the Montreal Cognitive Assessment (MoCA) score) (28), and the use of antidepressants or anxiolytic / hypnotic agents were confounding variables. Significant confounding was defined as a change in the regression coefficient of 10% or more. To assess whether sleep problems at baseline predicted anxiety after six months of follow-up, this analysis was repeated with the STAI total score as the dependent variable. To evaluate the inverse temporal relationship between these variables, we performed a logistic regression analysis with the presence of insomnia (0 = insomnia not present, 1 = insomnia present) as the dependent variable, and either severity of depression or anxiety at baseline as independent variables.

Alpha was set at $p < 0.05$. We present the crude model (Model 1) and the model adjusted for baseline value of the outcome variable (Model 2). For the final linear regression models we calculated the regression coefficient (B) with standard error (SE), standardized regression coefficient (β), 95% confidence interval and p-value. For the multinomial regression analyses we will report the odds ratio (OR) with its 95% confidence interval and p-value.

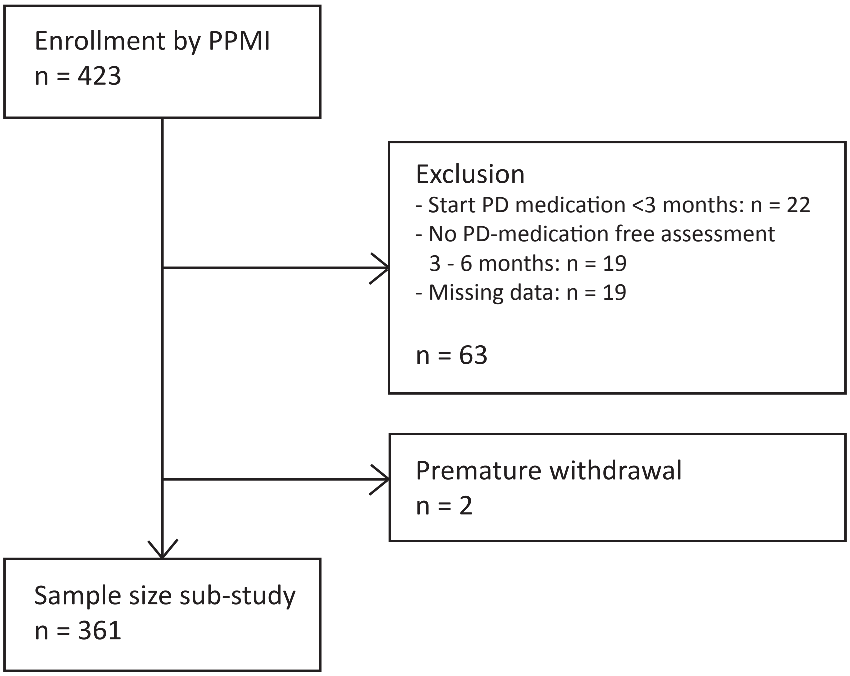
Assumptions for regression analyses (normality and homoscedasticity of residuals) were checked. Multicollinearity was evaluated using the variance inflation factor (VIF). As a sensitivity analysis, we assessed whether there were significant differences in demographic and clinical characteristics at baseline between the included and excluded participants, using t-tests for continuous variables and Chi^2-tests for categorical variables.

Results

Subjects

A flow chart of the study is presented in Figure 1. The total sample size of this sub-study consisted of 361 subjects.

Figure 1: **Flow chart.**



n = number, PPMI = Parkinson's Progression Markers Initiative, PD = Parkinson's disease

As a sensitivity analysis, we compared the proportion of males and females, mean age, and mean total baseline score of the STAI, GDS-15, MDS-UPDRS section III and MDS-UPDRS item 1.7 for subjects that were included and excluded. There were no significant differences between these groups.

Demographic and clinical characteristics of the study population are presented in Table 1. The prevalence of insomnia at baseline was 23.0%. Clinically relevant symptoms of anxiety and depression were present in 3.6% and 14.0% of subjects, respectively.
At baseline, the GDS-15 and STAI score had a moderate positive correlation ($r = 0.65$, $p < 0.01$). The MDS-UPDRS III score had a weak positive correlation with the STAI score ($r = 0.12$, $p < 0.01$) and a weak negative correlation with the MoCA score ($r = -0.12$, $p < 0.05$). There were no significant correlations between the other baseline measures.

Table 1: **Demographic and clinical characteristics of the study population at baseline (n = 361).**

	% (n)	Mean (SD)	Range
Female	33.5% (121)		
Age (yrs)		61.8 (9.6)	34 – 85
MDS-UPDRS III score		21.0 (8.7)	4 – 51
H&Y stage			
Stage 1	42.2% (153)		
Stage 2	57.1% (206)		
Stage 3	0.6% (2)		
MoCA total score		27.1 (2.4)	17 – 30
STAI total score		64.9 (18.4)	40 – 137
STAI State score		32.7 (10.3)	20 – 76
STAI Trait score		32.2 (9.4)	20 – 63
Clinically relevant symptoms of anxiety	3.6% (13)		
GDS-15 total score		2.3 (2.5)	0 – 14
Clinically relevant symptoms of depression	14.1% (51)		
Clinically relevant symptoms of insomnia	23. 0% (83)		
Rating of sleep problems on MDS-UPDRS item 1.7:			
Missing	*0.3% (1)*		
Normal	48.2% (174)		
Slight	28.5% (103)		
Mild	15.2% (55)		
Moderate	5.3% (19)		
Severe	2.5% (9)		

MDS-UPDRS-III= Movement Disorders Society - Unified Parkinson's Disease Rating Scale, section III: Motor examination; H&Y = Hoehn & Yahr; MoCA = Montreal Cognitive Assessment; GDS-15 = 15-item Geriatric Depression Scale; STAI = State-Trait Anxiety Inventory

At follow-up, the prevalence of subjects with insomnia was 25.8%, with clinically relevant symptoms of anxiety and depression occurring in 4.2% and 18.6% of subjects. The mean STAI total score at follow-up was 66.0 ± 19.7, the mean GDS-15 score 2.7 ± 3.1. Thus, the frequency of insomnia and severity of symptoms of anxiety and depression increased slightly over the six-month period.

Relationship between insomnia and symptoms of depression and anxiety

Histograms demonstrated a positively skewed distribution of the residuals of the continuous outcome measures. As log transformation of the data only slightly improved normality of the distribution of the residuals of the STAI total score, we decided to use the original data for the analyses to maintain interpretability of results. Homoscedasticity was confirmed. The VIF ranged from 1.06 to 1.08, indicating non-collinearity of the data.

Baseline insomnia was not associated with STAI total score (B (SE) = 1.75 (1.81), $p = 0.33$) or GDS-15 total score (B (SE) = 0.49 (0.31), $p = 0.11$) at follow-up, after correcting the model for baseline scores of these independent variables (see Table 2). As a post hoc analysis, we repeated this analysis with the STAI State and Trait subscale scores at follow-up as dependent variables (see Table 3). While the association between baseline insomnia and STAI Trait score was not significant (B (SE) = -0.41 (0.87), $p = 0.64$), the presence of insomnia at baseline was a significant predictor for a higher STAI State score at follow-up (B (SE) = 2.50 (1.07), $p < 0.05$).

When looking at the reverse relationships, baseline symptoms of both STAI total (B (SE) = 0.02 (0.01), $p = 0.001$) and GDS-15 score (B (SE) = 0.15 (0.05), $p < 0.001$) were significantly associated with presence of insomnia after six months of follow-up (see Table 4). As a final post hoc analysis, we repeated this analysis with the baseline STAI State and Trait subscale scores as independent variables. Both baseline STAI State score (B (SE) = 0.04 (0.01), p <0 .01) and STAI Trait score (B (SE) = 0.05 (0.02), $p < 0.01$) were significantly associated with the presence of insomnia at follow-up (see Table S1 in the supplementary material).

The use of anxiolytic / hypnotic medication at baseline was a positive confounder in the association between baseline insomnia and GDS-15 total score and STAI Trait subscale score at follow-up. However, only two subjects used anxiolytic/hypnotic medication at baseline. In the other associations, no significant confounding occurred for sex, age, severity of motor symptoms, global cognitive functioning, the use of antidepressants or the use of anxiolytic / hypnotic agents (data not shown).

Table 2: **Results of the linear regression analysis with the STAI and GDS-15 total score at T1 as dependent variable, and the presence of insomnia at T0 as independent variable.**

Dependent variable →	T1 STAI total score				T1 GDS-15 total score			
Independent variable ↓	B (SE)	β	95% CI	p-value	B (SE)	β	95% CI	p-value
Model 1:								
Constant	63.67 (1.16)	-	-	-	2.39 (0.18)	-	-	
T0 Insomnia	10.46 (2.42)	0.22	[5.71, 15.20]	<0.001	1.52 (0.38)	0.21	[0.78, 2.26]	<0.001
Model 2:								
Constant	16.68 (2.70)	-	-	-	0.90 (0.18)	-	-	-
T0 insomnia	1.75 (1.81)	0.04	[-1.80, 5.30]	0.33	0.49 (0.31)	0.07	[-0.12,1.10]	0.11
T0 dependent variable	0.76 (0.04)	0.70	[0.68, 0.84]	<0.001	0.75 (0.05)	0.61	[0.65, 0.85]	<0.001

Table 3: **Results of the linear regression analysis with the STAI State STAI Trait subscale scores at T1 as dependent variables, and the presence of insomnia at T0 as independent variable.**

Dependent variable →	T1 STAI State score				T1 STAI Trait score			
Independent variable ↓	B (SE)	β	95% CI	p-value	B (SE)	β	95% CI	p-value
Model 1:								
Constant	31.81 (0.62)	-	-	-	31.83 (0.60)	-	-	
T0 Insomnia	5.56 (1.29)	0.22	[3.03, 8.09]	<0.001	4.82 (1.25)	0.20	[2.37, 7.27]	<0.001
Model 2:								
Constant	13.01 (1.47)	-	-	-	6.63 (1.27)	-	-	-
T0 insomnia	2.50 (1.07)	0.10	[0.40, 4.60]	<0.05	-0.41 (0.87)	-0.02	[-2.12, 1.30]	0.64
T0 dependent variable	0.60 (0.04)	0.58	[-0.02, 0.14]	<0.001	0.82 (0.04)	0.76	[0.74, 0.90]	<0.001

B = regression coefficient, SE = standard error, β = standardized regression coefficient, 95% CI = 95% confidence interval

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Table 4: **Results of the logistic regression analysis with presence of insomnia at T1 as dependent variable and STAI and GDS-15 total score at T0 as independent variable.**

Dependent variable →	**T1 insomnia**				Dependent variable →	**T1 insomnia**			
Independent variable ↓	B (SE)	OR	95% CI of OR	p-value	Independent variable ↓	B (SE)	OR	95% CI of OR	p-value
Model 1:					*Model 1:*				
Constant	-3.34 (0.48)	-	-		(Constant)	-1.58 (0.18)	-	-	-
T0 STAI total score	0.03 (0.01)	1.04	[1.01, 1.05]	<0.001	**T0 GDS-15 total score**	0.21 (0.05)	1.23		<0.001
Model 2:					*Model 2:*				
Constant	-3.40 (0.54)	-	-	-	(Constant)	-2.17 (0.22)	-	-	-
T0 STAI total score	0.02 (0.01)	1.03	[1.01, 1.04]	0.001	**T0 GDS-15 total score**	0.15 (0.05)	1.16	[1.05, 1.29]	<0.001
T0 insomnia	2.31 (0.30)	10.10	[5.62, 18.16]	<0.001	**T0 insomnia**	2.37 (0.30)	10.70	[5.99, 19.11]	<0.01

B = regression coefficient, SE = standard error, OR= odds ratio, 95% CI = 95% confidence interval

Discussion

Despite the frequent occurrence and negative impact of anxiety, depression and insomnia in PD patients, little is known about their temporal evolution. In non-PD samples, the relationship between insomnia, anxiety and depression has been studied extensively, leading to divergent hypotheses. The first hypothesis is that insomnia precedes depression and anxiety, and therefore can be viewed as a risk factor for depressive and anxiety disorders (14-17). The alternative hypothesis is that anxiety and depression cause a disturbance of sleep (15, 18). In PD patients, an association between insomnia and both depression and anxiety has been found in cross-sectional studies (5, 11-13), but this study design does not allow for conclusions on directionality. Therefore, in this study, we performed a bidirectional analysis on the relationship between insomnia and symptoms of depression and anxiety, using data obtained in the first six months of a prospective cohort study in early-stage, medication-naïve PD patients.

When testing the first hypothesis, we found that insomnia did not predict the severity of depressive symptoms anxiety after six months of follow-up. This is in contrast with multiple studies in the general population, where insomnia was found to be a risk factor for the development of a depressive disorder (16, 18). This difference may be explained by the fact that our study participants had relatively mild mood disturbances; the prevalence rate of clinically relevant symptoms of depression at follow-up was 18.6%, while the prevalence was 35% in PD samples that included subjects with a more advanced disease stage (6).

We also found that insomnia was no predictor for the severity of anxiety at follow-up. However, when differentiating between "trait" and "state anxiety, using the subscales of the STAI in a post hoc analysis, we found that baseline insomnia was a significant predictor for a higher STAI State subscale score at follow-up, while it was not for the STAI Trait subscale score. State anxiety refers to a transitory experience of anxiety, whereas trait anxiety is defined as the proneness to interpret internal stimuli or external events in such a way that results in anxiety (22). Trait anxiety can therefore be viewed as personality trait, which is stable over time, while state anxiety is more dynamic. This might explain why the presence of insomnia predicted a higher STAI State score, but had no significant association with the STAI Trait score at follow-up.

While longitudinal studies in PD patients on the association of insomnia and anxiety are lacking, our findings are in line with studies performed in the general population, where insomnia was found to increase the risk of developing an anxiety disorder (15, 29). Various studies indicate that sleep is of importance for maintaining adaptive emotional regulation and reactivity. Experimental sleep deprivation has been shown to result in enhanced physiological responses to negative stimuli (30). Riemann et al. (2012) hypothesized that a chronic fragmentation of REM sleep in insomnia might cause a disturbance of the emotional network, interfering with basal processes of emotion regulation(31). This hypothesis is supported by the results of a recent study, indicating that restless REM sleep interferes with overnight resolution of distress, which might contribute to the development of chronic hyperarousal (32). Insomnia may therefore lead to altered physiological and emotional responses, which facilitate the development of anxiety. In PD patients, degeneration of brainstem nuclei that are involved in sleep-wake regulation is thought to lead to a decreased REM stability (33). Moreover, PD patients are prone to sleep problems due to PD symptoms that interfere with sleep, and a vulnerability for a disturbed circadian rhythm (34). Insomnia may therefore play a role in the development or progression of symptoms of state anxiety in PD patients.

When testing our second hypothesis, we found that baseline symptoms of both state and trait anxiety and depression predicted the occurrence of insomnia six months later. This is in agreement with two epidemiological studies in the general population, where anxiety and depression were found to precede insomnia (15, 18). Various explanatory models for this association have been proposed. Acute insomnia is generally viewed as a result of an acute stressor in an individual that is prone to sleep disturbances due to trait factors, like a tendency to ruminate or a genetically determined dysfunction in sleep-wake regulating circuitries (35, 36). According to the behavioral model, maladaptive coping with sleep problems, like daytime napping and prolongation of time spent in bed, can contribute to the development of chronic insomnia. Moreover, conditioned arousal may act as a perpetuating factor, in which the sleep environment becomes a stimulus for arousal instead of rest (36). Conditioned arousal consists of cognitive (e.g. worrying about sleep problems and their consequences) and physiological symptoms. The interaction between these two types of arousal is thought to be mediated by heightened emotionality (36), i.e. affect-laden cognitions are more likely to interfere with sleep than neutral thoughts. In a synthesis of these models, insomnia can be viewed as a result of the interaction between increased emotional, cognitive and physiological arousal, or a ' psychobiological state of hyperarousal' (35).

In PD patients, one can imagine that having a chronic, progressive disease, which results in increasing disability over time, can cause negative cognitions and emotions, leading to psychological and physiological arousal and subsequent sleep problems. Our findings suggest that even subclinical symptoms of anxiety and depression (e.g. worrying or feeling tense after recently receiving a diagnosis of PD), can interfere with sleep in PD patients, and contribute to the development of insomnia.

Insomnia, depression and anxiety often co-occur in PD (5, 11-13), and insomnia is a symptom of both depression and some anxiety disorders, for instance generalized anxiety disorder. This may raise the question whether the associations we found can be explained by the fact that insomnia is an integral part of depression and anxiety disorders. However, since we used the GDS-15 and the STAI, which do not contain items on disturbed sleep (23, 25), there is no overlap between the measures used for anxiety and depression, and insomnia. Moreover, we corrected for baseline severity of the outcome variable in our analyses (i.e., we corrected for the presence of insomnia at baseline in the analyses on the association between baseline depression and insomnia at follow-up). We therefore feel confident that our results indicate that symptoms of state anxiety should be viewed as an independent risk factor for the development of insomnia in PD, and insomnia for increased symptoms of anxiety and depression.

To our knowledge, this is the first study to examine the longitudinal, bidirectional relationship between sleep disturbances and symptoms of anxiety and depression in PD patients. A strength of this study is that we studied a cohort of PD patients who were not yet using antiparkinsonian medication, ruling out interference of dopaminergic treatment in the association between sleep and anxiety and depression. On the other hand, the selection of a study sample of medication-naïve, early stage PD patients with relatively short follow-up also limits the generalizability of our results to the entire PD population. In PD patients, the occurrence of sleep disturbances, depression and anxiety increases with progression of the disease (4, 21). Indeed, the prevalence rates of clinically relevant symptoms of anxiety, depression and insomnia in our study sample were relatively low compared to other PD samples (4-8). The fact that the majority of our subjects had subclinical symptoms makes it difficult to draw definite clinical conclusions from the study. Replication of our findings, preferably in a sample of PD patients that has been followed for a longer time and therefore, on average, developed more severe symptoms of anxiety, depression and insomnia, is therefore necessary. Our results do, however, indicate that clinicians should be attentive to symptoms of anxiety in PD subjects reporting insomnia, and vice versa, for complaints of insomnia in PD patients with anxiety or depression. Secondly, our finding of a bidirectional association between insomnia and state anxiety suggests that both anxiety and sleep disturbances can start a negative spiral in PD patients, constituting of psychobiological hyperarousal, disturbed sleep, altered emotional and physiological responses, a more disturbed sleep, etc.

In conclusion, the results of our study indicate that symptoms of anxiety and depression can be a risk factor for the development of insomnia in PD. This finding provides a target for research on preventive measures in insomnia. The relationship between insomnia and anxiety is bidirectional, which suggests that both symptoms of anxiety and sleep disorders can start a negative spiral in PD patients, where one enhances the other. To break this negative spiral, independent clinical attention for these symptoms in PD patients is warranted.

Supplementary material

Table S1: **Results of the logistic regression analysis with presence of insomnia at T1 as dependent variable and STAI State and Trait subscale score at T0 as independent variable.**

Dependent variable →	T1 insomnia				Dependent variable →	T1 insomnia			
Independent variable ↓	B (SE)	OR	95% CI of OR	p-value	Independent variable ↓	B (SE)	OR	95% CI of OR	p-value
Model 1:					*Model 1:*				
Constant	-2.82 (0.43)	-	-		(Constant)	-3.27 (0.46)	-	-	-
T0 STAI State score	0.05 (0.01)	1.05	[1.01, 1.07]	<0.001	**T0 STAI Trait score**	0.07 (0.01)	1.07	[1.05, 1.09]	<0.001
Model 2:					*Model 2:*				
Constant	-3.11(0.49)	-	-	-	(Constant)	-3.29 (0.52)	-	-	-
T0 STAI State score	0.04 (0.01)	1.04	[1.02, 1.06]	<0.01	**T0 STAI Trait score**	0.05 (0.02)	1.05	[1.01, 1.09]	<0.01
T0 insomnia	2.38 (0.30)	10.75	[6.00, 19.45]	<0.001	**T0 insomnia**	2.32 (0.30)	10.15	[5.65, 18.32]	<0.001

B = regression coefficient, SE = standard error, OR= odds ratio, 95% CI = 95% confidence interval

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5

Chapter 5

The effect of psychotherapy on psychological distress in patients with Multiple Sclerosis, Parkinson's disease and Huntington's disease: a meta-analysis

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Under review

Abstract

Objective

Psychological distress has a high impact on quality of life in patients with multiple sclerosis (MS), Parkinson's disease (PD), and Huntington's disease (HD). Studies have shown that cognitive behavioral therapy and mindfulness-based therapies are successful in reducing psychological distress in patients with anxiety and depressive disorders, and patients with chronic somatic diseases. We aimed to investigate the effectiveness of these treatment types in MS, PD, and HD patients.

Methods

We performed a comprehensive literature search in PubMed, PsycInfo, Embase and the Cochrane Central Register of Controlled Trials up to March 2018. Randomized controlled trials (RCTs) investigating a psychological intervention and reporting psychological outcome measures were included. Two separate meta-analyses were performed; one in studies comparing the psychological intervention with a treatment as usual or waitlist condition and one in studies with another active treatment condition as comparator.

Results

The first meta-analysis (n = 12 studies, 8 in MS and 4 in PD populations) showed a mean effect size of $g = 0.51$. The second meta-analysis (n = 7 studies, all in MS populations) showed a mean effect size of $g = 0.36$. No RCTs were found in HD populations. The overall quality of the included studies was insufficient and considerable heterogeneity was found. No evidence was found for publication bias.

Conclusion

Psychological interventions have a small to moderate effect on reducing psychological distress in patients with PD and MS. However, more research with better methodological quality and larger study samples is warranted, especially in HD and PD patient populations.

Introduction

Progressive neurological disorders, such as Multiple Sclerosis (MS), Parkinson's disease (PD) and Huntington's disease (HD), are often accompanied by psychological distress (1-3). Psychological distress symptoms have a higher impact on the quality of life of both the patients and their caregivers than the physical symptoms (4, 5). The resemblance between MS, PD and HD includes the progressive nature of the disease, uncertainty on disease course, and incurability (only symptom reduction is possible), which contribute to psychological distress. Besides these elements, psychological distress can also arise from physical symptoms (such as spasms, rigidity, and autonomic dysregulation), resulting in a vicious circle where physical and psychological symptoms reinforce one another. In addition, neural circuits are affected by the disease (i.e. frontostriatal circuits), causing disruptions in cognition, affect, motivation, behavior, and stress regulation (6, 7). Because of these similarities, it is likely that these three patient populations can equally benefit from psychological treatments. This hypothesis is supported by the finding that a standardized psychosocial selfmanagement program proved to be effective in a variety of chronic diseases, including MS, PD, and HD (8).

A considerable number of studies has investigated potential effective treatments for stress reduction. In an extensive review and meta-analysis of Hofmann and colleagues (9), cognitive behavioral therapy (CBT) showed to be an effective treatment for general distress and, more specifically, anxiety symptoms in patients with psychiatric and medical conditions. Besides classical CBT, problem solving and self-management therapies are also considered CBT-based since these interventions are based on the same principles. In PD patients, CBT also showed positive effects in treating anxiety and depressive symptoms (10-12). In MS, Dennison et al. (13) concluded that CBT is effective in improving the management of somatic symptoms and psychological distress. According to Novak and Tabrizi (14), depression and anxiety are usually treated with medication in HD patients, but CBT is also effective in well-selected patients. However, these recommendations for HD patients are mostly based on expert opinion.

Besides CBT, mindfulness-based treatments (MBTs) receive increasing attention in clinical practice. Mindfulness involves paying attention in a particular way: on purpose, in the present moment, and non-judgmentally (15). MBTs include mindfulness-based stress reduction, mindfulness-based cognitive therapy, meditation, and acceptance and commitment therapy. MBTs have been proven to be effective in reducing anxiety and depression symptoms in patients with anxiety and depressive disorders (16), and patients with chronic pain (17). Also, small to moderate effect sizes in improving mental health were found in populations with different chronic somatic diseases (18, 19), and medium effect sizes were found in MBTs for MS patients (20).

To reduce psychological distress in patients with progressive neurological disorders, CBTs and MBTs might thus be of potential benefit. Since these interventions are considered treatment options, it is warranted to investigate their effectiveness. In order to establish the efficacy of CBTs and MBTs on reducing psychological stress in PD, HD, and MS patients, we performed a meta-analysis on randomized controlled trials.

Methods

Selection of studies

A comprehensive literature search was conducted in PubMed, PsycInfo, the Cochrane library and EMBASE through March 2018. In addition, *ClinicalTrials.gov* was searched for completed but unpublished studies. The following keywords were used: "Parkinson", "Huntington", "Multiple Sclerosis", "psychological distress", "stress reduction", "distress", "depressive symptoms", "anxiety symptoms" (see the supplementary material for the complete search string). Besides the database searches, recent meta-analyses (21-23) were read to find additional studies. Two researchers (IG, SR) independently selected the studies for inclusion and when they disagreed a consensus was made.
Inclusion criteria for the meta-analysis were: a study population of PD, HD, or MS patients, availability of an English or Dutch abstract or manuscript, the examination of a psychological intervention, availability of anxiety, depressive, or general psychological distress outcome measures, availability of data of each study allowing the calculation of standardized mean differences (post-treatment means, standard deviations, and number of participants, or other statistics that allowed to calculate effect sizes). Only randomized controlled trials (RCTs) were included in this meta-analysis.

Data extraction

All decisions on the inclusion of outcome measures, including depressive and anxiety symptoms and/or general mental health outcome measures, were based on consensus between two researchers (IG, SR). Outcome measures of psychological distress were extracted by these two researchers, independently. Post-treatment measurements were collected to examine the immediate effect of the interventions. When data was not available, the researchers of that particular study were contacted. In addition, two independent researchers (RB, MH) rated the type of interventions (CBT or MBT) investigated in the studies, based on the treatment components described in the manuscript.

Quality assessment

The methodological quality of the included studies was assessed with seven criteria of the risk of bias assessment tool, developed by Cochrane (24) to assess sources of bias in RCTs:

1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and researchers (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Other bias

Criterion 3 was impossible to meet due to the nature of psychotherapeutic studies on psychotherapeutic interventions, and was therefore always considered as biased. When questionable or unclear risk of bias was found, this was considered a risk of bias.
Again, quality assessment was performed by two independent researchers (IG, SR).

Meta-analyses

The Hedges' *g* effect sizes were calculated for each study and pooled with Comprehensive Meta-analysis (CMA; version 3 for Windows). Post-treatment means and standard deviations measures at post-treatment were used to calculate Hedges' *g*. Means and standard deviations from anxiety, mood, and general mental health outcome measures within each study were pooled so that one 'psychological distress' measure for each study was included in the meta-analyses. Two separate main meta-analyses were conducted: the first to investigate psychological interventions that were compared with waitlist or TAU conditions, the second to investigate psychological interventions that were compared with other active interventions (such as supportive listening, relaxation, and psycho-education).

Within the first main meta-analysis, besides the combined psychological distress measure, the individual effect sizes on anxiety, mood, and general mental health outcomes were investigated using separate meta-analyses. Subgroup analyses were conducted for disease type, control condition, and high vs low risk of bias. In addition, the relationship between risk of bias and effect size was investigated with a regression analysis. Within the second main meta-analysis, the different types of interventions of interest (CBTs and MBTs) were investigated by performing two separate meta-analyses. There were too few studies to perform further subgroup analyses.

As considerable heterogeneity was expected, all analyses were conducted using the random effects model. The I^2 statistic was calculated as an indicator of heterogeneity. We calculated the 95% confidence intervals (95% CI) around I^2 (25) using the non-central chi-squared based approach within the heterogi module for Stata (26). When the I^2 estimate reached 40%, this was classified as considerable heterogeneity (27).

Subgroup analyses were conducted according to the mixed-effects model (28), and the meta-regression analysis was conducted according to the procedures developed by Borenstein et al. (28).
Publication bias was examined with Duval and Tweedie's trim and fill procedure (29), as well as Egger's test for the asymmetry of the funnel plot.

Results

Selected studies

After removing duplicate studies, 156 records were found. After inspection of the titles and abstracts, 24 full-text articles were retrieved. In addition, four studies were included from past meta-analyses, resulting in 28 full-text articles that were read. Figure 1 presents the flowchart of the inclusion process with reasons for exclusion, following the PRISMA statement (30). Eventually, 19 studies were included, of which 12 were included in the first meta-analysis, and seven in the second meta-analysis.

Characteristics of included studies

Table 1 shows the characteristics of the included studies, displayed separately for the two main meta-analyses. Within the first analysis, eight studies included MS patients (31-37), four studies included PD patients (38-41), and no RCTs were found investigating HD populations. Nine studies examined a CBT-based intervention (31, 33-38, 40, 41) and three studies investigated an MBT (32, 39, 42).

Within the second analysis, only MS patients were investigated in the included studies. Regarding the treatments of interest, four studies investigated a CBT-based treatment (43-46) and three examined an MBT (47-49).

Overall, the quality of the included RCTs was suboptimal, based on the scores on the risk of bias assessment tool. As allocation concealment was often not well reported, two studies had a risk of detection bias (40, 47). The study by Okai et al. (40) also showed an attrition bias, as did the study by Calleo et al. (38). In the first analysis, four studies showed good quality (31, 33, 41, 42), as shown by a total risk of bias of 1 (only risk of performance bias). In the second analysis, only the study by Carletto et al. had good quality (49).

Figure 1: **PRISMA flow chart of selection and inclusion process.**

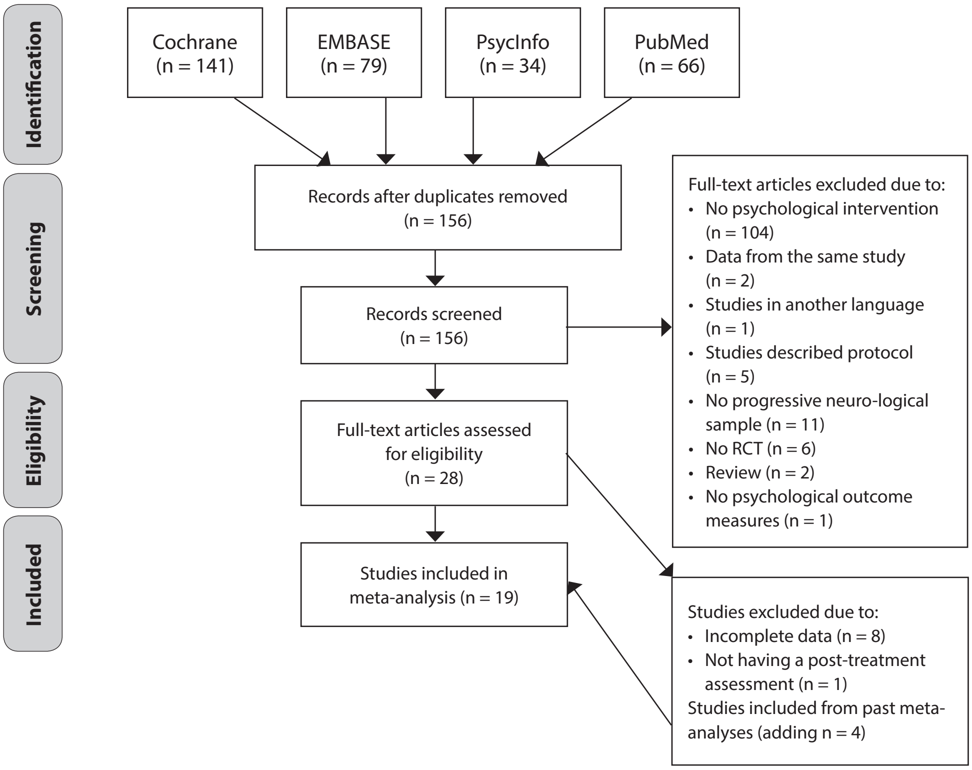


Table 1: **Study characteristics.**

Study	Medical condition	Comorbidity	Primary outcome	N intervention	Intervention	N control	Control	Outcomes in analysis	Risk of bias (0-7)*
Meta-analysis 1									
Forman et al. (2010)	MS	Anxiety and/or depressive symptoms	HADS & GHQ	20	CBT	20	WL	HADS-A HADS-D	0-?-1-0-0-0-0 (2)
Fischer et al. (2013)	MS	Depressive symptoms	BDI-II	45	CBT	45	WL	BDI-II	0-0-1-0-0-0-0 (1)
Bogosian et al. (2015)	MS	Psychological distress	GHQ	19	Mindfulness	21	WL	GHQ HADS-A HADS-D	0-?-1-0-0-0-0 (2)
Calleo et al. (2015)	PD	Anxiety and/or depressive symptoms	Feasibility & satisfaction	10	CBT	6	TAU	HADS-A HADS-D	0-0-1-0-1-?-0 (3)
Lincoln et al. (2011)	MS	Anxiety and/or depressive symptoms	GHQ	72	CBT	79	WL	BDI GHQ HADS-A HADS-D	0-?-1-0-0-0-0 (2)
Okai et al. (2013)	PD	Impulse control disorder(s)	NPI	28	CBT	17	WL	GHQ	?-0-1-1-1-0-0 (3)
Mohr et al. (2000)	MS	Moderate depressive symptoms	POMS-DDS	16	CBT	16	TAU	POMS-DDS	?-?-1-?-0-1-0 (5)
Ghielen et al. (2016)	PD	Anxiety symptoms	GSES	19	ACT+PT	19	TAU (PT)	BAI BDI	0-0-1-0-0-0-1 (2)
Troeung et al. (2014)	PD	Anxiety and/or depressive symptoms	DASS	11	CBT	7	WL	DASS-A DASS-D DASS-S	0-0-1-0-0-0-0 (1)
Boeschoten et al. (2016)	MS	Moderate/severe depressive symptoms	BDI-II	85	IPST	86	WL	BDI-II HADS-A BAI	0-0-1-0-0-0-0 (1)
Kiropoulos et al. (2016)	MS	Depressive symptoms	BDI-II	15	CBT	15	TAU	BDI-II STAI	0-0-1-1-0-0-0 (2)
Simpson et al. (2017)	MS	No inclusion criteria	PSS	25	MBSR	25	WL	PSS	0-0-1-0-0-0-0 (1)

Table 1, continued

Meta-analysis 2									
Oreja-Guevera et al. (2015)	MS	Unknown	HADS	21	MBSR	20	PE	HADS-A	Not assessable
Moss-Morris et al. (2013)	MS	Psychological distress	GHQ	48	CBT	46	SL	GHQ	0-0-1-0-0-?-0 (2)
Ehde et al. (2015)	MS	Fatigue, pain, or depressive symptoms	PHQ	75	Self-management	88	PE	PHQ	0-0-1-0-0-0-1 (2)
Nordin et al. (2012)	MS	Anxiety and/or depressive symptoms	HADS	11	ACT	10	Relaxation	BDI HADS-A HADS-D	0-?-1-1-0-0-0 (3)
Mohr et al. (2001)	MS	Major depressive disorder	HRSD & BDI	20	CBT	22	Supportive expression	BDI HRSD	1-?-1-?-0-0-? (5)
Mohr et al. (2005)	MS	Moderate depressive symptoms	HRSD & BDI-II	62	CBT	65	Supportive expression	BDI-II HRSD	1-?-1-0-0-0-0 (3)
Carletto et al. (2017)	MS	Depressive symptoms		43	BAM	45	PE	BDI-II, BAI, PSS	0-0-1-0-0-0-0 (1)

MS = Multiple Sclerosis, PD = Parkinson's Disease, CBT = Cognitive Behavioral Therapy, MBSR = Mindfulness Based Stress Reduction, ACT = Acceptance and Commitment Therapy, IPST = Internet-based Problem Solving Therapy, BAM = Body-Affective Mindfulness, PT = Physical Therapy, WL = Waitlist, PE = Psycho-Education, SL = Supportive Listening, TAU = Treatment As Usual, HADS = Hospital Anxiety and Depression Scale (A = anxiety, D = depression), , HRSD = Hamilton Rating Scale for Depression, BDI = Beck Depression Inventory, PSS = Perceived Stress Scale, GHQ = General Health Questionnaire, PHQ = Patient Health Questionnaire, NPI = NeuroPsychiatric Inventory, POMS = Profile Of Mood Scale, GSES = General Self-Efficacy Scale, BAI = Beck Anxiety Inventory, SE = Standard Error

Treatment Effects

Meta-analysis 1: psychological intervention versus TAU or waitlist condition

Figure 2 displays the forest plot of the standardized effect sizes of psychological interventions on psychological distress in PD and MS patients, compared with a waitlist or TAU condition. The mean effect size (*g*) was 0.51 (95% CI = 0.22 – 0.80) with a heterogeneity estimate (I^2) of 66 (95% CI = 27 – 80).

As a post-hoc analysis, the studies of Okai et al. (40), Ghielen et al. (37), and Kiropoulos et al. (33) were excluded in a separate meta-analysis. These studies were considered outliers since the effect sizes with their 95% confidence intervals were outside the 95% confidence interval of the pooled main effect size. The effect size decreased to *g* = 0.31 (95% CI = 0.13 – 0.48) and heterogeneity decreased to I^2 = 0 (95% CI = 0 – 56) when these three studies were removed (see table 2).

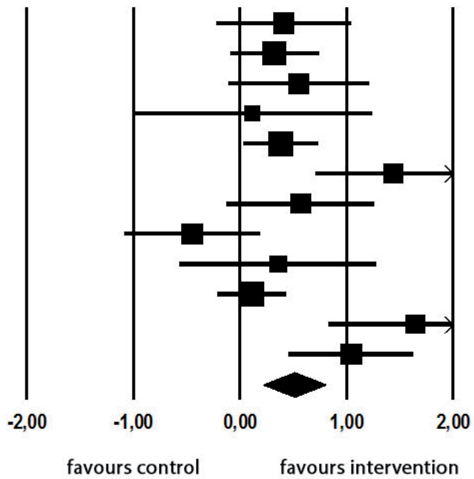
To investigate the treatment effects on the different types of outcome measure separately, three meta-analyses were conducted on anxiety, mood, and general psychological distress outcome measures. The treatment effect on general mental health outcomes was highest (*g* = 0.79, 95% CI = 0.32 – 1.25 with I^2 = 66, 95% CI = 0 – 85), followed by the effect on anxiety symptoms (*g* = 0.36, 95% CI = 0.03 – 0.66 with I^2 = 59, 95% CI = 0 – 79), and depressive symptoms (*g* = 0.33, 95% CI = 0.05 – 0.62 with I^2 = 60, 95% CI = 0 – 78) (see Table 2).

In addition, subgroup analyses were conducted (Table 2) to investigate differences in effect size for disease type, control condition, and risk of bias (high versus low). Significantly larger effect sizes were found in MS patient populations, TAU control condition, and studies with a high risk of bias. Meta-regression analyses on risk of bias (β = 0.08, 95% CI = -0.18 – 0.33, $p > 0.05$) did not show a significant relationship with effect size.

Figure 2: **Forest plot of studies comparing psychological intervention with treatment as usual (TAU) or waitlist (WL) conditions.**

Study name	Disease	Outcome	Statistics for each study			
			Hedges's g	Lower limit	Upper limit	p-Value
Forman et al. (2010)	MS	Combined	0,41	-0,22	1,04	0,201
Fischer et al. (2015)	MS	BDI	0,32	-0,09	0,74	0,124
Bogosian et al. (2015)	MS	Combined	0,55	-0,10	1,20	0,098
Calleo et al. (2015)	PD	Combined	0,11	-1,01	1,24	0,843
Lincoln et al. (2011)	MS	Combined	0,38	0,04	0,73	0,031
Okai et al. (2013)	PD	GHQ-12	1,44	0,71	2,17	0,000
Mohr et al. (2000)	MS	POMS DDS	0,57	-0,12	1,26	0,107
Ghielen et al. (2016)	PD	Combined	-0,45	-1,08	0,18	0,164
Troeung et al. (2014)	PD	Combined	0,36	-0,56	1,27	0,448
Boeschoten et al. (2016)	MS	Combined	0,11	-0,21	0,42	0,505
Kiropoulos et al. (2016)	MS	Combined	1,64	0,83	2,46	0,000
Simpson et al. (2017)	MS	PSS	1,04	0,46	1,62	0,000
			0,51	0,22	0,80	0,001

Hedges's g and 95% CI



Meta Analysis

Table 2: **Effect sizes and heterogeneity measures for psychological treatments in improving psychological distress in PD and MS patients, including subgroup analyses.**

	N (studies)	Hedges'*g*	95% CI	I²	95% CI	p-value	NNT*
Meta-analysis 1							
All	12	0.51	0.22 – 0.80	66	27-80	<0.01	3.55
Excluding outliers@	8	0.31	0.13 – 0.48	0	0-56	<0.01	5.75
Outcome							
Depression	10	0.33	0.05 – 0.62	60	0-78	<0.05	5.43
Anxiety	8	0.36	0.03 – 0.68	59	0-79	<0.05	5.00
Psychological distress	5	0.79	0.32 – 1.25	66	0-85	<0.05	2.36
Subgroup analyses							
Disease type							
MS	8	0.54	0.26 – 0.82	45	0-72	<0.01	3.36
PD	4	0.37	-0.55 – 1.29	80	16-91		4.85
Control condition							
Waitlist	7	0.39	0.18 – 0.60	26	0-68	<0.01	4.59
TAU	5	0.67	-0.16 – 1.49	82	49-91		2.75
Risk of Bias #							
High	8	0.57	0.14 – 0.99	71	22-84	<0.01	3.18
Low	4	0.42	0.02 – 0.81	61	0-85		4.27
Meta-analysis 2							
All	7	0.36	0.13 – 0.58	40	0-74	<0.01	5.00
Treatment type							
CBT	4	0.45	0.26 – 0.64	0	0-73	<0.01	3.55
Mindfulness	3	0.06	-0.56 – 0.68	68	0-89	ns	29.41

MS = Multiple Sclerosis; PD = Parkinson's Disease; CBT = Cognitive Behavioral Therapy; NNT = Number Needed to Treat; TAU = treatment as usual; ns = non-significant

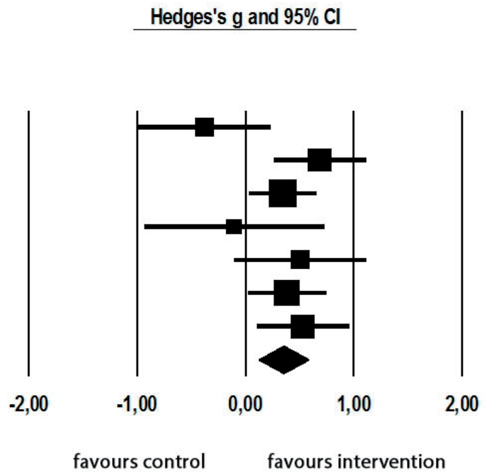
*according to Kraemer & Kupfer (50)
@ outliers include Okai et al. (40), Kiropoulos et al. (35), Ghielen et al. (39)
# low risk of bias include studies scoring 1 according to the risk of bias assessment tool, developed by Cochrane (24), a score > 1 is considered high risk of bias.

Meta-analysis 2: psychological intervention versus active control condition

Figure 3 shows the forest plot of the standardized effect sizes of psychological interventions on psychological distress in MS patients, compared with an active control condition. The mean effect size (*g*) was 0.36 (95% CI = 0.13 - 0.58) with a heterogeneity estimate (I^2) of 40 (95% CI = 0 - 74).

Figure 3: **Forest plot of studies comparing psychological interventions with active control conditions.**

Study name	Disease	Outcome	Hedges's g	Lower limit	Upper limit	p-Value
			Statistics for each study			
Oreja-Guevera et al. (2015)	MS	HADS-A	-0,37	-0,98	0,23	0,226
Moss-Morris et al. (2013)	MS	GHQ-12	0,69	0,27	1,12	0,001
Ehde et al. (2015)	MS	PHQ-9	0,35	0,04	0,66	0,026
Nordin et al. (2012)	MS	Combined	-0,10	-0,93	0,73	0,810
Mohr et al. (2001)	MS	Combined	0,51	-0,10	1,11	0,099
Mohr et al. (2005)	MS	Combined	0,39	0,03	0,74	0,033
Carletto et al. (2017)	MS	Combined	0,53	0,11	0,96	0,013
			0,36	0,13	0,58	0,002



Meta Analysis

To investigate the treatment effects for the types of investigated intervention, two separate meta-analyses were conducted on CBT-based treatments and MBTs. The treatment effect for CBT-based treatments was highest (*g* = 0.45, 95% CI = 0.26 – 0.64 with $I^2 = 0$, 95% CI = 0 – 73), followed by a small effect for MBTs (*g* = 0.06, 95% CI = -0.56 – 0.68 with $I^2 = 68$, 95% CI = 0-89) (see Table 2).

Publication bias

No evidence for publication bias was found in both meta-analyses. Inspection of the funnel plots did not indicate significant publication bias (Figures 4 and 5). Duval & Tweedie's trim-and-fill procedure did not result in the imputation of studies according to a random model. In addition, Egger's regression intercept indicated no significant publication bias (p > 0.05 in both analyses).

Figure 4: **Funnel plot of meta-analysis 1: psychological interventions versus treatment as usual (TAU) or waitlist (WL) conditions. The imputed studies are shown in black.**

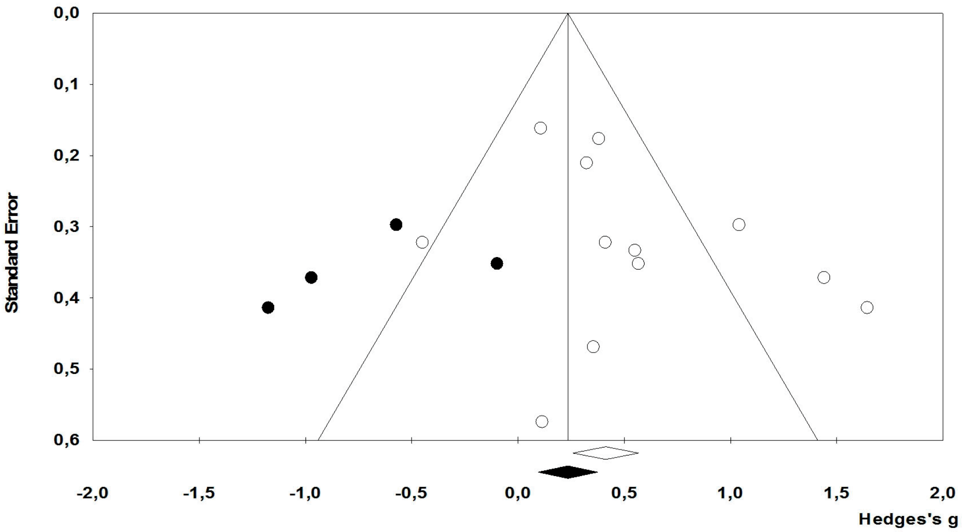
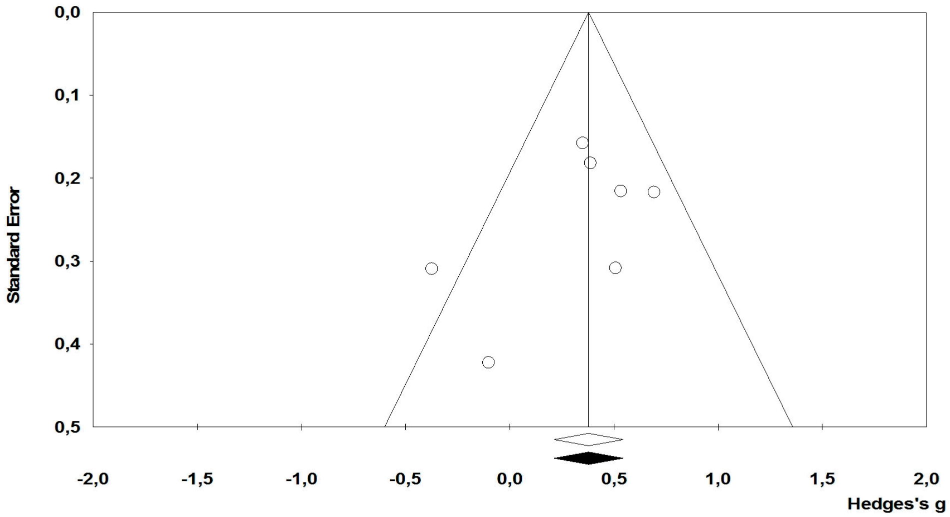


Figure 5: **Funnel plot of meta-analysis 2: psychological intervention versus active control condition.**



Discussion

In this study, we investigated the effectiveness of psychological interventions on psychological distress in patients with PD and MS by conducting a meta-analysis of randomized controlled trials. There were no RCTs found studying psychological interventions in HD populations. Nineteen studies were included in the analysis, of which twelve compared the treatment of interest with a TAU or waitlist condition (meta-analysis 1), and seven studies compared the treatment of interest with an active control condition (meta-analysis 2). A moderate effect size (g = 0.51) was found in the first meta-analysis, and a small effect size (g = 0.36) was found in the second meta-analysis. In both meta-analyses there was considerable heterogeneity, which is probably due to the variability in hours of treatment, different delivery forms (for example by telephone or face-to-face), and differences in comorbidity in the included subjects over all included studies. The heterogeneity decreased when outliers were removed, when depression and anxiety outcomes were analysed separately, when only looking at MS patient samples, when studies with waitlist control conditions were analysed, and when studies with a low risk of bias were analysed. In these post-hoc analyses, the effect sizes decreased to small (g = 0.31, g = 0.33, g = 0.36, g = 0.39, g = 0.42, respectively). No evidence was found for publication bias.

The small to moderate main effect sizes suggest that psychological interventions are beneficial in reducing psychological distress, but only to a certain extent. Biological

approaches, e.g. pharmacotherapy, showed a reduction of depressive symptoms in MS patients with an effect size of 0.63 (standardized mean difference) (22). According to the review and meta-analysis by Fiest et al. (2016), current research is insufficient to determine the effectiveness of pharmacotherapy for anxiety in MS as no controlled studies were found. In PD, the meta-analysis of Bomasang et al. (51) on antidepressant medication showed an effect size of 0.54 in reducing depressive symptoms. The effect of pharmacotherapy on reducing symptoms of anxiety in PD patients has insufficiently been studied. Although the effect sizes of pharmacotherapy on depressive symptoms appear to be larger than those of psychological treatment, in anxiety and global mental health the effect is not yet investigated properly. One can imagine that pharmacological interventions show larger effect sizes compared to psychotherapeutic interventions, since the latter requires cognitive abilities to learn and apply the methods that are taught. Although patients with dementia were excluded in most studies, it is possible that these populations have reduced cognitive abilities as a result of the neurodegenerative process, and are therefore unable to optimally benefit from CBT and MBTs. It is also argued that a combination of psychotherapy and pharmacotherapy might be most beneficial, at least for outpatients with chronic forms of depression (52, 53) and panic disorder (53). In adults with an anxiety or depressive disorder without neurological comorbidity, a meta-analysis of Cuijpers et al. (54) showed that CBT is probably effective. Although effect sizes were larger (around $g = 0.80$) compared to our results, the quality of the included studies was unsatisfactory and publication bias was present. Large effect sizes were also found for MBTs in the treatment of anxiety and depressive symptoms (55). Here, no publication bias was present but study quality was again unsatisfactory. CBT and MBTs appear to be more effective in patients without compared to patients with neurodegenerative disorders. However, the methodological quality is insufficient to draw definite conclusions.
The MS population is best represented in this meta-analysis, including fifteen RCTs of which eight were included in the first meta-analysis. The second meta-analysis included only studies in MS populations. Overall, the mean age of MS patient groups is lower compared to the PD patient groups. One can imagine that having a progressive neurological disorder in an earlier or later phase of life results in different psychosocial issues. However, all treatments described here were adapted to the respective study sample and no significant subgroup difference in effect size was found regarding disease type.

A considerably large effect size was found in the pilot study of Okai et al. (40). In this study, all PD patients additionally suffered from impulse control disorders. When the treatment components were critically investigated, it was notable that this was the only CBT-based intervention that included executive dysfunction education. PD patients often show an impairment in executive functioning in an early stage of the disease (56, 57). Since this study showed a great improvement in psychological distress, this might indicate that executive dysfunction plays an important role in regulating negative emotions and cognitions, at least in PD patients with impulse control disorders. This has to be confirmed in future research, however.

The pilot study by Kiropoulos et al. (35) also showed a large effect size (*g* = 1.64). This study included newly diagnosed MS patients (< 5 years since diagnosis) and the age of these patients was lower compared to other studies that investigated MS populations. These patients might be less severely affected compared to other study populations. Comparisons, however, could not be made since studies reported different measures of disease severity. No differences were found concerning treatment components when compared with other CBT-based interventions in MS.

An important factor is the focus of the treatment types and control conditions. The studies by Ghielen et al. (39), Oreja-Guevera et al. (48), and Nordin et al. (47) investigated MBTs. The first three studies showed (non-significant) negative effect sizes of *g* = -0.45, *g* = -0.37, and *g* = -0.10, respectively, favoring the control condition in reducing psychological distress symptoms. The focus of ACT is not on symptom reduction but on coping with the disease despite of the symptoms that are present. This is achieved by improving awareness of ones bodily sensations, thoughts and feelings. When one is more aware of his/her symptoms, these will also be more often reported, resulting in a higher score on questionnaires. In addition, these studies all included an active form of control condition: physical therapy (TAU), psycho education, and relaxation.

Another discussion concerns the suitability of questionnaires to measure treatment effects. Since MBTs are focused on awareness and acceptance, and not aim to reduce symptoms, questionnaires that measure the prevalence or severity of symptoms are less appropriate. The studies by Bogosian et al. (32) and Simpson et al. (42), however, investigated mindfulness interventions and showed effect sizes of *g* = 0.55 and *g* = 1.04, respectively, in improving general mental health . In addition, when overall psychological distress was measured with general mental health questionnaires, a high effect size of *g* = 0.79, although with considerable heterogeneity, was found. The focus of an intervention, type of control condition, and the outcome measures used seem to be of importance in evaluating the effectiveness, and therefore need to be carefully considered when conducting an RCT.

Overall, the investigated studies had insufficient quality, only three out of seventeen studies reached good quality. The findings need to be carefully interpreted since risk of bias is present in most of the studies and might have influenced the treatment effects. It is different for each study what types of bias might be present, except for the performance bias which is always a risk due to the nature of these intervention studies.

Limitations and implications

First, the effect size is solely based on studies in patients with PD and MS, since there were no RCTs found in HD that investigated the effect of psychological interventions on psychological distress. Second, MS patients might be overrepresented in the meta-analysis since fifteen out of nineteen RCTs investigated MS populations, resulting in the effect size being driven mostly by MS populations, especially in the second meta-analysis in which only MS populations were included.

Heterogeneity estimates were above 40% in most analyses, reflecting high heterogeneity within the meta-analyses, and most studies included small sample sizes, which resulted in low power.

Finally, the overall quality of the studies was insufficient and the quality of one study could not be assessed. It is therefore recommended to study psychological interventions in more detail and in larger patient samples in study designs with higher methodological quality. Especially HD is in need of more research, since no RCTs on the effects of psychological treatment were found in our literature search.

Next to a primary focus on reducing psychological distress, it would be interesting to investigate the effect on coping with the disease, quality of life, or self-efficacy, especially in trials studying the effect of MBTs. Since progression of the disease is inevitable, it is therefore important to learn how to cope with the disease instead of focusing on symptom reduction only. Furthermore, caution is warranted in the choice of outcome measures and the type of control conditions as comparators, since these decisions greatly influence the effect of the intervention of interest. Lastly, it might be interesting to increase attention towards executive dysfunction education in interventions for PD patients with impulse control disorders.

Conclusion

Despite the abovementioned limitations, we conclude that psychological interventions have a small to moderate effect on reducing psychological distress in patients with PD and MS. However, more research is warranted, especially in HD and PD patient samples. These studies need to have better methodological quality and study samples should be larger.

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6

Chapter 6

Bright light therapy in Parkinson's disease: an overview of the background and evidence

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Abstract

Sleep disorders are common in Parkinson's disease (PD) and seem strongly associated with depression. It has been suggested that sleep disorders as well as depression are caused by a disturbed circadian rhythm. Indeed, PD patients are prone to misalignment of their circadian rhythm due to various factors, and many patients with PD display a phase advance of their circadian rhythm. Current treatment options for sleep disorders and depression in patients with PD are limited and can have serious side effects; alternative treatments are therefore badly needed. Bright Light Therapy (BLT) restores circadian rhythmicity effectively in mood- and sleep-disturbed patients without PD. The few studies that focused on the efficacy of BLT in patients with PD not only demonstrated a positive effect of BLT on sleep and mood but also on motor function. More research on the neurobiology and efficacy of BLT in PD is warranted.

Introduction

In addition to the characteristic motor symptoms, patients with Parkinson's disease (PD) experience many non-motor symptoms, comprising a variety of cognitive, autonomic, sensory, neuropsychiatric and sleep disturbances (1, 2). Sleep disturbances and disorders (as defined in Table 1) including reduced total sleep time, reduced sleep efficiency, increased sleep fragmentation, Rapid Eye Movement (REM)-sleep behavior disorder, and excessive daytime sleepiness, occur in about 60-95% of PD patients (3-6). Sleep influences motor symptoms. The so-called 'sleep benefit', an improvement of motor functions upon awakening that occurs in more than 40% of PD patients, is attributed to improved dopaminergic function as a result of increased storage of dopamine in nigrostriatal terminals during sleep (7). Moreover, melatonin, a hormone secreted by the pineal gland at night, has been suggested to worsen motor symptoms in PD patients (8).

Sleep disorders in PD often coincide with depression (6). Depression occurs in 35-50% of patients throughout the course of the disease (9, 10). It has a major impact on overall functioning of PD patients: depressed PD patients score lower on scales assessing activities of daily living and exhibit more cognitive problems (9, 11, 12).

Sleep disorders and depression are two of the most important factors influencing quality of life of PD patients and their caregivers (4, 9, 13, 14). Unfortunately, treatment options are limited, and adding pharmacological agents raises non-adherence in PD patients (15). Moreover, medication can induce serious side effects in PD patients. Hypnotic drugs, often prescribed for sleep disorders, worsen daytime sedation and the risk of falling and are therefore less suitable for PD patients (16). Melatonin might ameliorate subjective sleep disturbances in PD patients, but objective improvement of sleep quality is minimal (17, 18). Since a number of studies indicate that melatonin has unfavorable motor effects through interaction with dopamine pathways, more research is warranted on the effects of exogenous melatonin in PD patients (19-22).

Tricyclic antidepressants (TCAs), used in the treatment of depression in PD, can cause orthostatic hypotension, sedation, cognitive, and anticholinergic adverse effects, in addition to extrapyramidal adverse effects, that may potentially worsen motor symptoms (23, 24). Results of studies focussing on the tolerability of selective serotonin reuptake inhibitors (SSRIs) are inconclusive (23-25). Levodopa treatment can alleviate nocturnal akinesia and thus improve sleep, but can conversely negatively influence sleep by reducing the duration of REM-sleep and increasing REM-sleep latency (26). Anticholinergics and dopamine agonists increase the risk of nighttime hallucinations (27). The latter are also associated with sudden attacks of daytime sleepiness (26), which may hamper quantity and quality of night-time sleep. Behavioral and psychotherapeutic interventions are often less feasible due to cognitive dysfunction and dementia (28). It is evident that there is a great need for an effective and patient-friendly alternative for treating sleep disorders and depression in PD patients.

Sleep problems and depressive symptoms often co-occur in PD (6, 14). Dysfunction of the biological clock might be a common underlying causal factor for these disorders, providing a promising potential target for treatment (29, 30). Bright light therapy (BLT) restores circadian rhythmicity and therefore effectively treats affective disorders and insomnia, and increases sleep efficiency (31-38).

Table 1: **Definitions of sleep terminology.**

Term	Definition
Sleep disturbance	Sleep pattern divergent of what is considered to be normal as objectively measured, for example by polysomnography.
Sleep disorder	Medical disorder involving sleep, resulting in suffering or reduced functioning, including dyssomnias and parasomnias.
Sleep onset latency	Time interval between time of turning of the lights and onset of sleep.
Sleep efficiency	Ratio of the time spent asleep to the amount of time spent in bed.
Chronotype	Individual internal timing type regarding preferred time for mental and physical activity and sleep.
Homeostatic sleep drive	Drive to sleep that gradually increases with prolonged wakefulness and decreases during sleep.
Sleep fragmentation	Disrupted sleep cycle due to interruption of a sleep stage, as a result of the appearance of a lighter sleep stage or wakefulness.
Sleep phase advance	Forward shift of the sleep/wake rhythm, as demonstrated by the time of the nocturnal elevation of plasma melatonin.
Insomnia	Sleep disorder comprising difficulty initiating and/or maintaining sleep or non-restorative sleep for at least one month, resulting in significant distress and/or impaired daytime functioning
REM-sleep behavior disorder	Parasomnia characterized by 'acting out' of dreams during REM-sleep due to absence of normally occurring muscle atonia.
Excessive daytime sleepiness	Parasomnia characterized by excessive sleepiness during the day, often with hypersomnia and the occurrence of sleep attacks.
Periodic limb movement disorder	Sleep disorder characterized by involuntary limb movements causing fragmented sleep.
Restless legs syndrome	Syndrome characterized by unpleasant sensations in one or more limbs, exacerbated by rest and relieved with activity, paired with a strong urge to move the affected limbs, often with paresthesias or dysesthesias.

Additionally, it might lead to improvement of motor symptoms in PD (8, 39, 40). BLT has few contraindications and side-effects and may therefore be an elegant alternative for the treatment of PD-related depression and sleep disturbances.

This article gives an overview of the neurobiology of the biological clock and the factors that contribute to its desynchronization in PD. Furthermore, we review the evidence for BLT as a treatment for sleep disorders, depression and motor symptoms in patients with PD, and provide recommendations for administration of BLT.

The circadian rhythm and consequences of desynchronization

To understand the effects of BLT, one needs to understand the (patho)physiology of circadian rhythmicity, as explained in this section. The circadian rhythm is generated by the circadian pacemaker, a group of about 10,000 neurons located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Its endogenous rhythm is slightly different from the 24-hour day-night cycle and has to be entrained by signals (or 'zeitgebers') such as light, activity and food (41). Light provides the 'daytime' signal, by exciting specialized melanopsin containing ganglion cells in the retina, that project towards the SCN via the retinohypothalamic tract (42). The output signals of the SCN convey circadian timing information to brain areas regulating behavior, body temperature, autonomic and neuroendocrine systems, including the secretion of melatonin by the pineal gland (42). The secretion of melatonin is inhibited by the SCN during the light cycle, but the SCN also contains melatonin receptors that inhibit SCN firing, thereby creating a negative feedback loop (43, 44).

Desynchronization of the biological clock can be caused by a variety of factors that influence the input of the SCN (45). A disturbed circadian rhythm is probably a major common causal factor in both depression and sleep problems (29, 46, 47). Some of the major neurotransmitters implicated in mood regulation, including serotonin, norepinephrine and dopamine, as well as their receptors, show a circadian rhythm in their levels, release and activity (48). Various polymorphic variations of clock genes such as TIM, BMAL1 and PER2 are associated with mood disorders (29). Research on the diurnal variability of mood has shown that misalignment of the circadian rhythm can induce mood changes (47). Some patients with a depressive disorder display a phase advance in circadian rhythm, as exhibited by a shift in melatonin and cortisol rhythms (36, 47). Dysfunction of the circadian clock can lead to sleep fragmentation or insomnia (42, 45).

The interaction between sleep and depression likely comprises more than a failure of the biological clock. Insomnia or hypersomnia are well-known symptoms of depression, but sleep disturbances can cause depressive symptoms as well (29, 47, 49-55). Emotional hyperarousal may increase autonomic activity, resulting in sleep difficulties (53). This is confirmed by the fact that depressed patients show altered sleep architecture, which normalizes after successful treatment (50). On the other hand, emotionality is frequently negatively toned in insomnia and poor sleep (47, 51) and studies on sleep deprivation showed enhanced emotional physiological responses to negative stimuli (49, 52, 55). During REM-sleep, emotional intensity of previous affective experiences is decreased (54, 56, 57). Functional Magnetic Resonance Imaging (fMRI) studies show that sleep deprivation leads to increased activation of the amygdala in response to negative aversive stimuli (58-60). These findings strongly suggest that sleep is relevant for maintaining adaptive emotional regulation and reactivity (29, 54).

In short, sleep disturbances and depression seem to be highly correlated. A disturbed biological rhythm might be a common underlying factor, and therefore an important starting point for treatment. However, the directionality of the relationship between these three remains uncertain and more research on this subject is warranted.

Desynchronization of the circadian rhythm in Parkinson's disease

PD patients are prone to desynchronization of their biological clock due to various factors that will be discussed in this section. The neurodegenerative process in PD leading to dopamine depletion is one of the underlying causes, since recent research links dopamine directly to the circadian rhythm (61-63). Striatal dopamine metabolism seems to be regulated by clock proteins such as PER2 (62). Reciprocally, stimulation of dopamine receptors affects the rhythm of expression of clock genes such as PER1 and PER2 in the striatum (61, 63). Dopamine also regulates the rhythmic expression of melanopsin in retinal ganglion cells, thereby influencing the entrainment of the circadian rhythm by light (64).

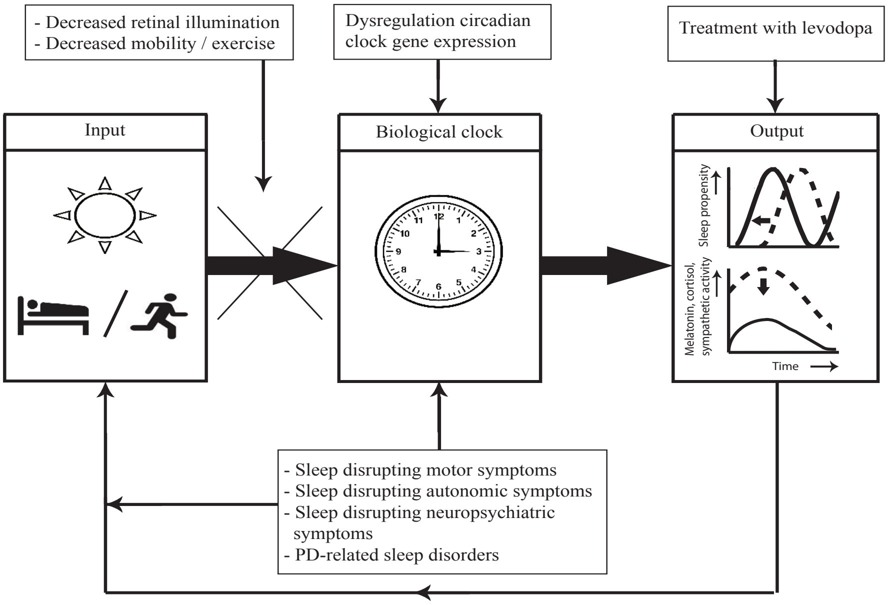
In many patients with PD, factors hampering the SCN input contribute to desynchronization of the circadian rhythm. Firstly, exposure and sensitivity to zeitgebers decrease. Retinal illumination decreases in the elderly due to pupillary miosis and reduced crystalline lens light transmission, especially of short wavelengths (65). This leads to partial light deprivation of the SCN and pineal gland. Additionally, PD patients, just like many elderly patients, may be more inclined to stay indoors due to motor problems or a decreased postural balance, and expose themselves less to environmental light and physical activities (45). Entrainment of the circadian rhythm is thwarted by a decreased exposure to zeitgebers.

The amplitude of the circadian rhythm decreases in patients with PD, as reflected by a decrease in sympathetic activity during the day, diminishing of the diurnal variation of cortisol secretion and a decrease of the amplitude of the melatonin secretion rhythm (19, 66, 67). This flattening of circadian rhythms makes them more prone to desynchronization. Sleep in PD patients can be disrupted by both motor (e.g. nocturnal akinesia and dystonia) and non-motor symptoms such as nocturia (1, 68). Additionally, PD patients may experience periodic limb movement disorder, restless legs syndrome, REM-sleep behavior disorder and excessive daytime sleepiness (4, 26, 68), all contributing to a reduced quality and/or quantity of sleep. PD-related neuropsychiatric disorders such as benign hallucinations and psychosis can also disturb sleep (6). Emotional stress, caused by having a progressive neurodegenerative disorder that increasingly results in disability, may interact with the basic homeostatic and circadian drives for sleep through the interaction between affect-related regions and regions that control sleep and wake (30). A disturbed sleep-wake cycle results in conflicting SCN input.

Finally, pharmacological treatment of PD with dopaminergic drugs also influences sleep/wakefulness mechanisms. Levodopa use can lead to a decrease of sympathetic activity during the day and disappearance of the sympathetic morning peak (69). Levodopa influences sleep architecture, reducing the duration of REM-sleep and increasing REM-sleep latency (26).

All of the abovementioned factors may contribute to a desynchronization of the circadian rhythm in PD, as displayed in Figure 1. In several small studies, levodopa treated PD patients display a phase-advanced circadian rhythm compared to healthy controls and de novo PD patients (19, 70, 71), making them vulnerable to depression and sleep disorders. Indeed, PD patients have more frequent awakenings at night and a reduced sleep efficiency compared to healthy controls (68). BLT acts as a strong zeitgeber and may therefore restore circadian rhythmicity in PD patients.

Figure 1: **A proposed model for the dysregulation of the circadian system in Parkinson's disease.**



The input of the biological clock by zeitgebers is both decreased and conflicted due to various motor and non-motor symptoms in PD. Dopamine depletion due to PD disrupts circadian clock gene expression, and its treatment with levodopa influences both sleep structure and sympathetic activity. These factors all alter output of the biological clock: there is a phase advance and flattening of the circadian rhythm as displayed by hormone levels and sympathetic activity. In turn, the alteration of circadian rhythmicity has a negative influence on (input of) the biological clock, leading to a downward spiral resulting in sleep disturbances and depression.

Efficacy of bright light therapy

In the last couple of years, research on the efficacy of BLT has shifted from adults to the elderly and specifically to PD patients. In 2005 a meta-analysis demonstrated that BLT is effective in treating seasonal affective disorder (SAD) and non-seasonal depression in adults, with effect sizes equivalent or superior to psychopharmacologic treatment (31). BLT has few side-effects and is therefore considered a patient-friendly treatment (32, 72).

Two recent large randomized controlled trials focused on the efficacy of BLT for non-seasonal depression in elderly (32, 33). Lieverse et al. (2011) stated that the positive effects of BLT were due to improved circadian rhythmicity, as displayed in their study by 1) an increased steepness of the evening rise of salivary melatonin levels, 2) a reduction of 24-hour urinary cortisol excretion, and 3) a trend-significant accelerated diurnal decline in salivary cortisol levels (32). Riemersma – van der Lek et al. (2008) demonstrated that

BLT attenuated cognitive and functional decline and positively influenced mood in 189 residents of group care facilities, of which 87% had dementia (33). In this study, BLT only improved sleep when it was combined with the administration of melatonin. In other studies, BLT as monotherapy was effective in improving both sleep efficiency and quality and in reducing daytime sleepiness in elderly patients with and without dementia (32, 34, 35, 37).

To summarize, BLT seems to be effective in treating sleep disorders as well as depression. Most of the abovementioned studies, however, excluded patients with disorders such as PD. Only four studies have addressed the use of BLT in PD (8, 39, 40, 73); these will be discussed in the following section. The first study in which BLT was used in PD patients is only available in Russian and is therefore not included in this overview (73).

Willis and Turner (2007) described a case series of 12 patients with PD and insomnia and/or depressive symptoms (40). They used BLT of 1000-1500 Lux for 60 to 90 minutes prior to normal bedtime during two to five weeks. Of the eight participants that reported significant problems with falling asleep, seven showed improvement in the onset and continuity of sleep after BLT treatment. Most patients reported this effect within two to three days after commencing BLT, and this lasted for several days after discontinuation. Six of 11 patients showed a noticeable improvement of mood. The antidepressant effect lasted for several weeks, even after discontinuation of BLT, and was paralleled by increased socialization. BLT resulted in improved motor function in most PD patients, with the strongest effects on bradykinesia and rigidity. After BLT, dopamine replacement therapy was reduced to a level ranging from 13 to 100% in five subjects, while antidepressants and hypnotic drugs were reduced or eliminated in two patients. Younger patients, especially those that were medication-naïve, responded better to BLT than those over 75 years of age, and adherent patients had a better therapeutic response than those who used it intermittently.

In a RCT by Paus et al. (2007), 18 PD patients treated with BLT of 7500 Lux were compared to 18 PD patients receiving placebo light of 950 Lux (39). Light was administered for 30 minutes in the morning during two weeks. PD-related symptoms were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS), depression was measured with the Beck Depression Inventory (BDI). Patients who received BLT showed a significant improvement on UPDRS sections I (evaluation of mentation, behavior, and mood), II (self-evaluation of the activities of daily life) and IV (Hoehn and Yahr Scale) compared with the control group. Improvement of UPDRS I and II did not correlate with changes in BDI scores, implying that the effects of BLT on behavior and daily functioning were independent of changes in mood. There was no significant difference on UPDRS section III (clinician-scored motor evaluation), except for a slight attenuation of tremor. Regarding sleep, the only sleep parameter investigated was a one-item daytime sleepiness scale, which did not show a between group difference. Mood improved significantly, but moderately, in the BLT group, as demonstrated by an average decrease of 2.2 points on the BDI. No significant improvement of BDI scores occurred in the control group. The short treatment duration and the fact that only mildly depressed patients were included might explain the modest effects of BLT on motor function and depression.

Willis et al. (2012) performed a retrospective, open label study monitoring 129 levodopa-treated PD patients for a period ranging from a few months to eight years (8). These patients were all prescribed BLT at a dose of 4000 to 6000 Lux for one hour prior to bedtime. Depending on the degree of adherence, PD patients were divided in the early quit group (EQUIT; patients that withdrew from BLT immediately after intake), the adherent group and the semi-adherent group. Twelve patients suffering from other neurological conditions served as a control group. Motor function was assessed with three timed motor tests and with a global rating scale. Psychiatric symptoms and sleep were evaluated on a global rating scale during an interview. Total drug burden (TDB) was determined and monitored over time. There was a slight deterioration of insomnia seen in EQUIT patients, while adherent patients showed an acute and dramatic improvement. Adherent patients displayed a significant improvement of bradykinesia, rigidity, balance and motor tests, while the motor parameters in the EQUIT group deteriorated over time. In the semi-adherent group, these parameters varied over time and appeared associated with periods of non-adherence with BLT or changes in drug regimen. All groups displayed an improvement of depression over time, with the most robust improvement seen in adherent patients. Anxiety did not change in the EQUIT group in contrast to other groups, with the greatest improvement in the adherent group. The adherent and semi-adherent groups required an increase in TDB in respectively 13 and 15% of cases, while 91% in the EQUIT group required increased medication. Moreover, patients in the EQUIT group were on similar doses of dopamine replacement therapy as the other PD patients, but displayed more severe PD than those who received BLT. In the adherent group, morbidity improved over the course of years, while in the EQUIT group, progression of PD severity was as expected. Limitations of this study are the fact that the study was not blinded or placebo-controlled, and that patients were monitored for different periods of time. Depression can lead to psychomotor retardation (74), so the improvement of motor function in these studies could be attributed to a decrease in depressive symptoms. However, in the study by Paus et al. (2007) there was no improvement of motor function in the subjects that demonstrated a significant decrease of the BDI score (39). More likely, the positive effects of BLT on motor symptoms in PD result from a restored balance between melatonin and dopamine (8). A number of studies indicate that melatonin has unfavorable motor effects through interaction with dopamine pathways (19-22).

Another point that is not addressed in these studies is the effect of other zeitgebers on the improvement in circadian rhythmicity. All subjects were given BLT at a set time, prior to bedtime or after awakening in the morning. This may have improved the daily rhythm and sleep-wake cycle of participating patients. Behavioral and psychological interventions are also effective in treating insomnia (75, 76).

Taken together, these studies display a positive effect of BLT on mood, sleep, and motor functions in PD patients. However, since these studies were relatively small and suboptimally designed, further studies on the efficacy of BLT in treating both non-motor motor and motor symptoms in patients with PD are warranted.

Recommendations for administration of BLT

In this section, recommendations for administration of BLT as well as information on contraindications and adverse effects are provided. Due to a lack of research on BLT in PD patients, the majority of these recommendations are based on research in patients without PD, so we must stress that (adverse) effects in PD patients might be different. More research on the effects of BLT in PD patients needs to be done before BLT can be used for PD patients in daily clinical practice.

There are many types of light boxes available. Clinically tested models yield a maximum illuminance of 10.000 Lux at a comfortable sitting distance of about 30 cm (38, 77). At this intensity, a duration of 30 minutes per session is usually sufficient, while lower intensities require longer sessions (31, 78, 79). It is advisable to use a light box with a complete ultraviolet (UV) filter, since cumulative UV radiation can be harmful to eyes and skin (80, 81).

Time of administration of BLT depends on the nature of a patients complaints and his or her individual chronotype. Morning light advances the biological clock and has proven to be effective in treatment of depression (77, 78). However, patients with PD probably have a phase-advanced circadian rhythm, and one might argue that evening BLT might be more efficient (8, 19, 40, 70, 71). On the other hand, Paus et al. (2007) demonstrated that morning light can improve mood and sleep in PD patients as well (39).
BLT is most effective when administered relative to individual chronotype (38, 82). The chronotype can be assessed with the Morningness – Eveningness Questionnaire (MEQ), which correlates with the time of onset of evening rise in melatonin secretion and circadian variation of oral temperature (78, 82, 83). An online version of the MEQ at the website of the Center for Environmental Therapeutics (www.cet.org) contains a table of

the recommended timing of morning BLT based on the MEQ-score. Strict adherence to BLT is necessary to maximize efficacy (8).
There is no consensus on the total duration of treatment with BLT in non-seasonal depression or insomnia. In PD patients, follow-up after discontinuation of BLT was only performed in the study of Willis et al. (2007) (40). They observed that the antidepressant effect of BLT lasted after discontinuation of therapy, but sleep deteriorated after a couple of days. These findings correspond with a large study on the effects of BLT in elderly patients with a non-seasonal depression (32). Since it might take months before BLT can exert positive effects on motor function, a long treatment duration of PD patients might be necessary (8). More research on both timing and duration of BLT in patients with PD is warranted.

Cumulative light energy can cause damage to skin and eye tissues, especially short-wavelength UV light (78, 80, 81). Patients with porfyria, macular degeneration, retinal dystrophy, lupus erythematosus, chronic actinic dermatitis and solar urticaria can have photosensitization reactions to light, and should only receive BLT under monitoring of an ophthalmologist or dermatologist (78). Moreover, some pharmacological agents are known to photosensitize the skin or retina, including some of the tricyclic antidepressants, tetracyclic antibiotics and antiarrhythmic drugs (78). These medications should be stopped before commencing BLT.
In a study of 70 subjects receiving BLT for a SAD the most often reported adverse effects were headache, eye or vision problems and nausea (72). No oculoretinal changes were detected during ophthalmologic evaluations of patients receiving treatment with BLT to up to six years (84). Some cases of BLT-induced (hypo)mania have been described, requiring discontinuation of BLT and medication (72, 85, 86). However, in patients with a known or suspected bipolar disorder BLT can be administered when the patient is using a mood stabilizer (80). Nevertheless, side effects of BLT are mostly mild and usually resolve within a couple of days (32, 33, 72).

Conclusion

Sleep disturbances are common in PD and are strongly associated with depression (3-6). A disturbed circadian rhythm may be a common underlying factor in both disorders (29, 46, 47). PD patients are prone to misalignment of the circadian rhythm due to dopamine deficiency as well as various other factors that disrupt input to the SCN (1, 4, 26, 45, 63, 66, 68). Indeed, many patients with PD display a phase advance of their circadian rhythm (19, 70, 71), which may contribute to the increased prevalence of sleep disturbances and depression (6, 9, 10).

Since the current treatment options for sleep disturbances and depression in PD are limited and can have serious side-effects (16, 23), alternative treatments are badly needed. BLT restores circadian rhythmicity and is an effective treatment for depressive disorders and insomnia in the general population (31-35, 37). So far, little research has focused on the efficacy of BLT in patients with PD (8, 39, 40, 73). The studies that have been performed were small and suboptimally designed, yet demonstrated a positive effect of BLT on sleep and mood in patients with PD. Moreover, BLT may positively influence motor function, possibly through a restored balance between melatonin and dopamine (8, 40). It might thus facilitate a dose reduction of dopaminergic medication (8, 40). BLT has few side-effects and is therefore patient-friendly (32, 72). Nevertheless, more research is warranted to demonstrate the efficacy and underlying mechanism of BLT in PD.

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Chapter 7

Spectramax™ light therapy as adjuvant treatment of Parkinson's disease: a randomized clinical trial

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Under review

Abstract

Background
Previous studies suggest that LT may be effective for motor and non-motor features of PD.

Objective
To evaluate the safety and efficacy of Spectramax™ specialized light therapy (LT) as adjunctive treatment in Parkinson's disease (PD).

Methods
We performed a multi-center, double-blind, controlled clinical trial of LT in PD patients on stable dopaminergic therapy. Participants were randomized 1:1 to active treatment with Spectramax LT or control LT for 60 minutes daily for six months. The primary outcome was the change in Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II + III score. Prior to unblinding, the primary outcome was changed to include Part I to better reflect overall disease severity. Secondary outcomes were quality of life (PDQ-39), sleep (PDSS-2, ESS), clinical global impression of improvement (CGI-I) and individual MDS-UPDRS components.

Results
Ninety-two subjects (45 active, 47 control) were enrolled. The LSM difference (SE) for the MDS-UPDRS Part I + II + III change was 8.0 (4.4) ($p = 0.07$), and for Part II + III 5.4 (3.9) ($p = 0.17$). Spectramax LT significantly improved PDQ-39 ($p = 0.04$) and MDS-UPDRS Part I score ($p < 0.01$) with a trend for ESS score ($p = 0.05$). Adverse events were more common in the active group, but no serious adverse events were attributed to the intervention.

Conclusion
Spectramax LT is associated with a trend in improving PD symptom severity, although the benefit was not statistically significant. Given that Spectramax LT improved non-motor symptoms and quality of life, and was generally well tolerated, further investigation is warranted.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with the prevalence expected to double in the coming decade (1). Its clinical spectrum encompasses numerous motor and non-motor manifestations. However, the majority of available treatments target motor symptoms, and are often associated with adverse events. There is still a great need to advance the therapeutics of both motor and non-motor symptoms of PD.

Light therapy (LT) is a non-pharmacological, well-tolerated treatment widely available and utilized in sleep medicine and psychiatry (2-4). Several clinical studies have found beneficial effects of LT on PD symptoms, including sleep-wake cycle, mood, quality of life, and even motor symptoms (5-7). Similarly, there is evidence supporting beneficial effects of supplemental light exposure in animal models of PD (8, 9). The beneficial effects of LT in PD are thought to be mediated through its synchronizing effect on the circadian system (10). This system synchronizes behavioral and physiologic functions with cycles of day and night allowing for better physiological homeostasis.

Studies of LT in PD published to date have utilized a broad-spectrum light. This clinical trial examined effects of Spectramax™, a specialized LT device that emits narrow-bandwidth blue/green light, on the overall burden of PD symptoms.

Methods

Study design and procedures

This study was an international multi-center, double-blind, randomized-controlled trial to assess the efficacy of the Spectramax LT device on disease severity in PD, as compared to a control light device. The study protocol was approved by the Institutional Review Board or Ethics Committee of the study sites and registered on clinicaltrials.gov (NCT02175472).

Prospective participants completed a screening survey and authorization for the site to review their medical history and medication use. After the screening visit, participants fulfilling eligibility criteria were enrolled and randomized into either the active or control group in a 1:1 ratio in blocks of four participants, stratified by site. After randomization, baseline assessments were performed by a blinded assessor. Participants were required to wear an actigraphy watch and complete the Consensus Sleep Diary (CSD) for a period of two weeks (11). Thereafter, the study coordinator performed a home visit to collect the actigraphy watch and diaries and set-up the investigational device. Participants were treated at home for a period of six months, after which they entered a one-month follow-up period. Both subjects and assessors were blinded regarding the treatment allocation. To prevent unblinding, subjects were asked not to share any details of their treatment with their assessor.

Baseline study assessments were repeated one, three, and six months after the start of treatment, and after one month of follow-up. Subjects were assessed in the "ON" state. All assessments were performed in the clinic, with the exception of the diaries and actigraphy that were performed at home by the participant for two weeks during baseline, and preceding the month three and month six visits. When a participant was unable to visit the clinic, the assessor visited the participant at home. Between assessment visits, the study coordinator placed biweekly follow-up calls to the participant, to encourage treatment compliance and to record safety related events.

Participants

Participants were recruited at three sites: i) Amsterdam University Medical Centers (Amsterdam UMC), Amsterdam, the Netherlands, ii) Movement Disorders Unit, Massachusetts General Hospital, Boston (Massachusetts), USA, and iii) Aspen Clinical Research, Utah (Utah), USA. Recruitment took place through an advertisement and local patient communities. All participants provided written informed consent.

Eligible participants were diagnosed with idiopathic PD, Hoehn &Yahr (H&Y) stage II or III, and were on stable dopaminergic therapy. Participants were excluded if they had a co-morbid somatic or psychiatric disorder or cognitive impairment that could interfere with assessments. They had to be on a stable dose of psychoactive and dopaminergic medication for at least six weeks, with no anticipated required changes in dopaminergic medication during their study participation. Additional exclusion criteria were previous exposure to LT, shift work, anticipated multi-time zone travel, eye trauma or disease, participation in clinical trial 30-days prior to the baseline visit, the use of photosensitizing drugs, an age younger than 45 years, severe dyskinesias, and high total drug burden of dopaminergic medication (> 1,500 mg/day).

Intervention

The active group was treated with the Spectramax LT Lamp, a table-top LT device emitting blue/green narrow bandwidth LED light (λ = 450 - 570 nm, 950 Lux). Participants in the control group received a control light device that was physically identical to the experimental device, but emits broad bandwidth polychromatic light (λ = 430 - 780

nm, 100 Lux). At an intensity of 100 Lux, no substantial effect on circadian rhythmicity is expected (12). All participants were required to administer LT one hour daily, at a fixed time between 6 and 10 PM as chosen by the participant, ending at least one hour prior to bedtime. Total treatment duration was six months.
LT devices were tested and certified as "no risk" according to all international basic electrical safety, ocular safety and essential performance standards.

Outcomes

The initial primary outcome measure was the change in severity of PD, as measured with the score of Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (13), Part II + III, from baseline to the end of treatment. However, prior to unblinding the study and unlocking the database, the primary endpoint was changed to the change in score of MDS-UPDRS Part I + II + III from baseline to the end of treatment, in order to allow for better assessment of treatment effects on both the non-motor and motor aspects of the disease severity.

Secondary outcome measures were the change from baseline to the end of treatment for the following variables, with the first three prospectively designated as key secondary outcomes:

- Clinical Global Impression (CGI), Clinical Global Improvement subscale (CGI-I) (14).
- Health-related quality of life, assessed with the Parkinson's Disease Questionnaire 39 (PDQ-39) (15), Summary Index (PDQ-39-SI).
- Self-reported quality of sleep, assessed with the Parkinson's Disease Sleep Scale 2 (PDSS-2) (16), Disturbed Sleep subscale (PDSS-2-DS).
- Self-reported daytime sleepiness, assessed with the Epworth Sleepiness Scale (ESS) (17).
- Depressive symptoms, as measured with the Beck Depression Inventory, second version (BDI-II) (18).
- Symptoms of anxiety, as measured with the Beck Anxiety Inventory (BAI) (19).
- Self-reported motor symptoms and PD symptoms at night, assessed with the corresponding subscales of the PDSS-2 (16).
- Scores on the subscales of the PDQ-39.
- Individual components of the MDS-UPDRS: Part I (non-motor aspects of daily living), Part II (motor aspects of daily living), Part III (clinician-rated motor assessment), and Part IV (motor complications of dopaminergic medication) (13).
- CGI Severity Index (CGI-S) and Efficacy Index (CGI-E) (14).
- Number of symptoms and number of wearing-off symptoms, as measured with question 1 and 2 of the Q10 Questionnaire for Wearing-Off (Q10), respectively (20).

Safety and adverse events (AEs), as defined in ISO 14155:2011, were reported to the study coordinator during follow-up calls and the assessment visits. AEs were coded according to the ATC Organ Class classification. The CGI-E Side Effects question was used to inquire about the subjective experience of AEs. To assess ocular safety, participants underwent an eye exam, including assessment of the best corrected visual acuity and an Amsler grid test, by a trained physician at baseline and end of treatment.

Statistical analysis

All statistical analyses were performed with SAS version 9.4. Statistical significance was defined as a two-sided p-value of <0.05. Analyses were performed on the Modified-Intent-To-Treat (mITT) population, consisting of all enrolled participants who received at least one light treatment and provided at least one post-baseline efficacy measure. Demographics and clinical characteristics are presented with percentages or mean scores with standard deviations.

Efficacy analyses

Linear mixed model analyses were used to assess the differences on the outcome variables between the Spectrax LT and control group at the end of treatment. The linear mixed models included the intervention variable, time (treated as a categorical variable and represented by dummy variables), a time-by-intervention interaction, a correction for study site, and the baseline value of the particular outcome variable.

Safety analyses

Safety data are presented for all enrolled participants that had at least one light treatment (Safety population). Incidence rates of AEs were compared between groups with a two-sided Fisher's Exact test.

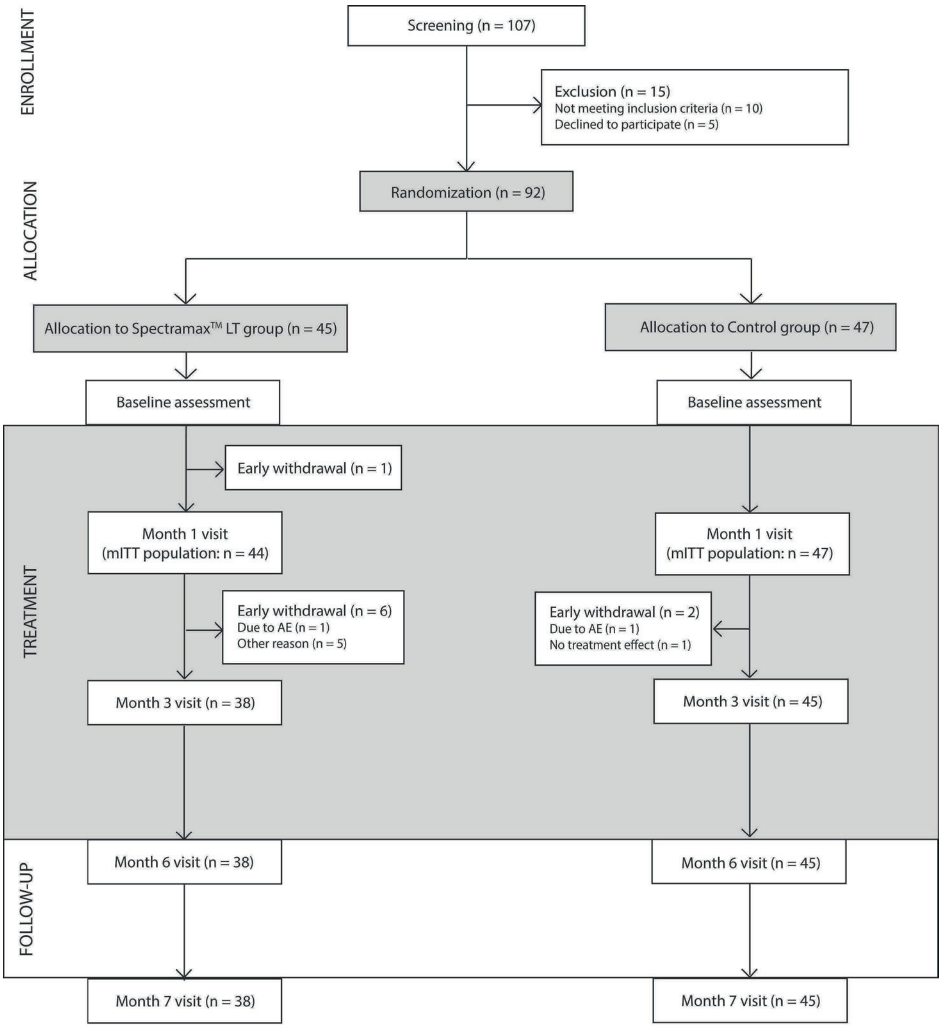
Sample size calculation

For a statistical power of 80% to detect a 50% reduction in the primary outcome from baseline to the end of treatment, with a coefficient of variation (standard deviation/mean) of 0.57 and a two-sided alpha of 0.05, we required 19 participants per group. Since the average treatment effect was only a crude approximation of the primary efficacy endpoint, and to accommodate possible drop-out, a more conservative sample size estimate of 40 patients per group was chosen. For details on the sample size calculation, see the supplementary material.

Results

The trial ran between July 2014 and September 2016. A flow chart of the study is presented in Figure 1. Of the 107 participants screened for eligibility, 10 did not meet inclusion criteria and five declined to participate. The proportion of eligible patients was higher than anticipated, resulting in a total study population of 92 participants. Forty-five participants were randomized into the active and 47 to the control condition. One participant in the active group did not have a post-baseline assessment visit, resulting in a mITT population of 91.

Figure 1: **Flow chart.**



AE = adverse effect, LT = light therapy, mITT = modified Intent-To-Treat, n = number

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Table 1: **Demographic and clinical characteristics of the mITT population at baseline.**

Variable	**Spectramax LT group (n = 44)**		**Control group (n = 47)**	
	Mean (SD)	**Mean (SD)**	**Range**	**Range**
Age	70.2 (8.0)	65.9 (7.6)	[52, 81]	[55, 85]
% female (n)	27.3% (12)	36.2% (17)		
% of patients per site (n)				
Utah (USA)	45.5% (20)	48.9% (23)		
Massachusetts (USA)	20.5% (9)	19.1% (9)		
Amsterdam (NL)	34.1% (15)	31.9% (15)		
% H&Y stage (n)				
Stage 1	2.3% (1)	2.1% (1)		
Stage 2	77.3% (34)	80.8% (38)		
Stage 3	20.5% (9)	17.4% (8)		
MDS-UPDRS				
Part I	11.6 (6.7)	12.1 (5.5)	[2, 24]	[0, 27]
Part II	14.9 (7.5)	16.0 (8.0)	[2, 35]	[3, 31]
Part III	39.8 (20.8)	37.1 (19.2)	[7, 86]	[3, 80]
Part IV	6.3 (5.4)	6.4 (5.1)	[0, 17]	[0, 16]
LED (mg/day)	650.7 (381.6)	613.3 (367.6)	[0, 1500]	[0, 1425]
MDS-UPDRS I + II + III	66.3 (31.3)	65.2 (29.6)	[23, 140]	[15, 130]
MDS-UPDRS II + III	54.7 (26.9)	53.1 (25.8)	[16, 119]	[8, 111]
BDI-II	8.2 (4.3)	8.3 (3.6)	[1, 13]	[0, 14]
BAI	10.4 (8.0)	10.6 (6.8)	[2, 31]	[0, 27]
PDSS-2 total	12.9 (7.6)	15.8 (7.9)	[1, 29]	[2, 34]
Disturbed Sleep	8.0 (3.8)	9.2 (4.4)	[0, 19]	[1, 17]
Motor symptoms	3.0 (3.6)	3.4 (2.9)	[0, 11]	[0, 13]
PD symptoms at night	1.9 (2.5)	3.2 (3.0)	[0, 10]	[0, 12]
ESS	9.4 (6.4)	8.4 (5.1)	[0, 22]	[0, 24]
CGI				
CGI-I	n.a.	n.a.	n.a.	n.a.
CGI-S	2.3 (1.4)	2.4 (1.5)	[1, 5]	[1, 5]
CGI-E	n.a.	n.a.	n.a.	n.a.
PDQ-39 SI	32.7 (20.7)	29.5 (19.3)	[4, 88]	[3, 80]
MOB	25.0 (21.7)	18.6 (18.9)	[0, 75]	[0, 78]
ADL	21.7 (19.3)	22.3 (19.2)	[0, 71]	[0, 75]
EMO	17.5 (18.3)	13.9 (14.0)	[0, 54]	[0, 71]
STI	18.0 (15.9)	11.6 (15.7)	[0, 75]	[0, 63]
SOC	8.3 (11.8)	8.2 (15.7)	[0, 50]	[0, 42]
COG	24.1 (17.4)	21.8 (15.3)	[0, 50]	[0, 81]
COM	19.9 (20.3)	24.8 (24.4)	[0, 100]	[0, 75]
BOD	26.5 (24.5)	34.0 (20.1)	[0, 75]	[0, 92]
Q10-1	5.6 (2.3)	5.5 (2.8)	[0, 10]	[0, 10]
Q10-2	0.4 (0.4)	0.5 (0.4)	[0, 1]	[0, 1]

Legend Table 1

USA = United States of America; NL = the Netherlands; H&Y = Hoehn & Yahr; LED = levodopa equivalent dose; H&Y = Hoehn & Yahr; MDS-UPDRS = Movement Disorders Society – Unified Parkinson's Disease Rating Scale; BDI-II = Beck Depression inventory II; BAI = Beck Anxiety Inventory PDSS-2 = Parkinson's Disease Sleep Scale 2; ESS = Epworth Sleepiness Scale PDQ-39 SI = Parkinson's Disease Questionnaire 39 Summary Index; MOB = mobility; ADL = activities of daily living; EMO = emotional wellbeing; STI = experienced stigma; SOC = social functioning; COG = cognition; COM = communication; BOD = bodily discomfort; Q10 = Questionnaire for Wearing-Off; CGI = Clinical Global Impression; CGI-S = CGI - Severity Index; CGI-E = CGI - Efficacy Index; CGI-I =CGI - Clinical Global Improvement; n.a. = not applicable

During treatment, five participants in the active condition withdrew due to issues with the daily time requirement, and one participant in the control group due to a lack of therapeutic effect. Two withdrew due to AEs.

An overview of the demographic and clinical characteristics of the mITT population at baseline is presented in Table 1. The mean (SD) age of study participants was 68.0 (8.0) years, and 32% were female. The mean MDS-UPDRS total score at baseline was 65.8 (30.3) with 79% HY stage 2 and 19% in H&Y stage 3.

Efficacy analyses

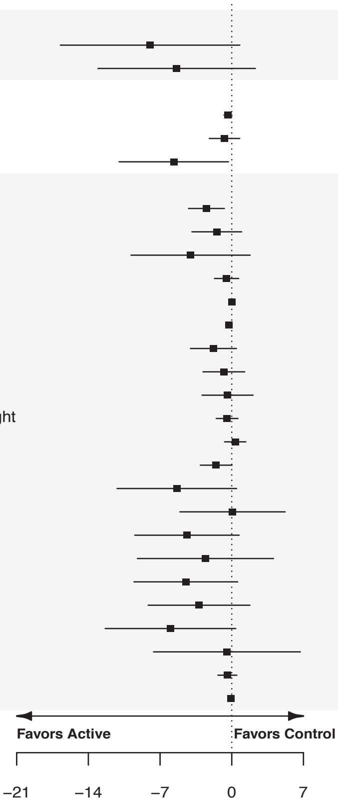
Results are graphically presented in Figure 2, with the data shown in Table 2. The change (SE) from baseline to the end of treatment in the revised primary outcome, the MDS-UPDRS Part I + II + III score, was 17.7 (2.8) for the active group versus 9.7 (3.4) for the control group (LSM difference = 8.0 (4.4); p = 0.07). There was also no significant between-group difference in the original primary outcome, the change in MDS-UPDRS Part II + III score (LSM difference (SE) = 5.38 (3.86), p = 0.17).
When looking at the key secondary outcomes, the PDQ-39 SI score improved significantly more with Spectramax LT (LSM difference (SE) = -5.7 (2.7), p = 0.04). The CGI-I score showed a trend in favor of the active group (LSM difference (SE) = -0.4 (0.2), p = 0.07). The between-group difference in PDSS-2-DS was not significant.

Of the other secondary outcomes, MDS-UPDRS Part I showed a significant between-group difference (LSM difference (SE) = -2.47 (0.88), p < 0.01), with a larger improvement in the Spectramax group compared to control group. The between-group difference in ESS score showed a trend in favour of the active group (LSM difference (SE) = -1.52 (0.78), p = 0.05), with a decrease in excessive daytime sleepiness (EDS) in the active group and a deterioration in the control group. The other secondary endpoints did not demonstrate significant between-group differences.

At baseline assessment, we found out that two participants had been incorrectly included because of an H&Y stage of I. As a *post hoc* analysis, we repeated the efficacy analyses excluding these two participants. There were significant between-group differences for the MDS-UPDRS Part I + II + III score (LSM difference (SE) = 9.1 (4.5); $p < 0.05$), the ESS (LSM difference (SE) = -1.6 (0.8), $p < 0.05$), and PDQ-39 (LSM difference (SE) = -6.2 (2.7), $p < 0.05$). There were no other changes in statistical significance of other outcomes.

Figure 2: **Graphical representation of the efficacy analyses.**

Graphical Summary



Test	p	Estimate [95% CI]
Primary outcome		
MDS UPDRS I+II+III	0.0740	–7.97 [–16.73 , 0.79]
MDS UPDRS II + III	0.1676	–5.38 [–13.06 , 2.30]
Key secondary outcomes		
CGI–I	0.0663	–0.37 [–0.76 , 0.02]
PDSS–2 Disturbed Sleep	0.3454	–0.71 [–2.19 , 0.78]
PDQ–39 Total	0.0381	–5.66 [–11.00 , –0.32]
Other secondary outcomes		
MDS UPDRS I	0.0061	–2.47 [–4.22 , –0.72]
MDS UPDRS II	0.2336	–1.46 [–3.89 , 0.96]
MDS UPDRS III	0.1729	–4.02 [–9.84 , 1.79]
MDS UPDRS IV	0.4021	–0.50 [–1.69 , 0.68]
CGI–S	0.8609	0.02 [–0.22 , 0.27]
CGI–E Therapeutic Effects	0.0880	–0.28 [–0.60 , 0.04]
BDI–II	0.1171	–1.79 [–4.03 , 0.46]
BAI	0.4537	–0.77 [–2.81 , 1.26]
PDSS–2 Total	0.7439	–0.41 [–2.90 , 2.08]
PDSS–2 Motor Symptoms at Night	0.4005	–0.45 [–1.52 , 0.61]
PDSS–2 PD Symptoms at Night	0.5226	0.34 [–0.70 , 1.38]
ESS	0.0538	–1.52 [–3.07 , 0.03]
PDQ–39 MOB	0.0713	–5.36 [–11.20 , 0.48]
PDQ–39 ADL	0.9767	0.08 [–5.06 , 5.21]
PDQ–39 EMO	0.0916	–4.37 [–9.47 , 0.72]
PDQ–39 STI	0.4439	–2.57 [–9.21 , 4.07]
PDQ–39 SOC	0.0818	–4.48 [–9.54 , 0.58]
PDQ–39 COG	0.2044	–3.19 [–8.16 , 1.77]
PDQ–39 COM	0.0654	–5.98 [–12.36 , 0.39]
PDQ–39 BOD	0.8961	–0.47 [–7.64 , 6.69]
WOQ 1	0.3601	–0.43 [–1.35 , 0.50]
WOQ 2	0.3189	–0.08 [–0.22 , 0.07]

Table 2: **Treatment effects on motor symptoms, mood, sleep and quality of life, for the mITT population.**

	LS Mean Change from Baseline				
	Spectramax LT	**Control**	**LSM difference**		
	Mean (SD)	*Mean (SD)*	*Difference (SE)*	*95% CI*	*p-value*
Primary outcome					
MDS-UPDRS I + II + III	-17.7 (2.8)	-9.7 (3.5)	-8.0 (4.4)	-16.7, 0.8	0.07
MDS-UPDRS II + III	-14.0 (2.6)	-8.6 (2.9)	-5.4 (3.9)	-13.1, 2.3	0.17
Key secondary outcomes					
CGI-I	-0.6 (0.1)	-0.2 (0.1)	-0.4 (0.2)	-0.8, 0.0	0.06
PDSS-2 Disturbed Sleep	0.0 (0.6)	0.7 (0.5)	-0.7 (0.7)	-2.2, 0. 8	0.35
PDQ-39-SI	-1.3 (2.1)	4.3 (1.7)	-5.7 (2.7)	-11.0, -0.3	**0.04**
Other secondary outcomes					
MDS-UPDRS					
Part I	-3.6 (0.5)	-1.1 (0.7)	-2.5 (0.9)	-4.2, -0.7	**<0.01**
Part II	-3.5 (0.8)	-2.1 (0.9)	-1.5 (1.2)	-3.9, 1.0	0.23
Part III	-10.4 (2.0)	-6.4 (2.2)	-4.0 (2.9)	-9.8, 1.8	0.17
Part IV	-1.3 (0.4)	-0.8 (0.5)	-0.5 (0.6)	-1.7, 0.7	0.40
CGI					
CGI-S	-0.1 (0.1)	-0.1 (0.1)	0.0 (0.1)	-0.2, 0.3	0.86
CGI-E Therapeutic	2.2 (0.1)	2.5 (0.1)	-0.3 (0.2)	-0.6, 0.0	0.09
BDI-II	-1.1 (0.7)	0.7 (0.9)	-1.8 (1.1)	-4.0, 0.5	0.12
BAI	-1.0 (0.6)	-0.3 (0.8)	-0.8 (1.0)	-2.8, 1.3	0.45
PDSS-2 total	0.2 (0.9)	0.6 (0.9)	-0.4 (1.3)	-2.9, 2.1	0.74
Motor symptoms	-0.3 (0.4)	0.1 (0.4)	-0.5 (0.5)	-1.5, 0.6	0.40
PD symptoms at night	0.4 (0.4)	0.0 (0.3)	0.3 (0.5)	-0.7, 1.4	0.52
ESS	-1.4 (0.6)	0.1 (0.5)	-1.5 (0.8)	-3.1, 0.0	0.05
PDQ-39 subscales					
MOB	1.3 (2.3)	6.6 (1.8)	-5.4 (2.9)	-11.2, 0.5	0.07
ADL	1.7 (2.1)	1.6 (1.5)	0.1 (2.6)	-5.1, 5.2	0.98
EMO	-3.8 (1.8)	0.6 (1.8)	-4.4 (2.6)	-9.5, 0.7	0.09
STI	-2.6 (2.2)	0.0 (2.4)	-2.6 (3.3)	-9.2, 4.1	0.44
SOC	-1.6 (1.3)	2.9 (2.2)	-4.5 (2.5)	-9.5, 0.6	0.08
COG	-2.2 (1.8)	1.0 (1.8)	-3.2 (2.5)	-8.2, 1.8	0.20
COM	-2.5 (2.4)	3.5 (2.2)	-6.0 (3.2)	-12.4, 0.4	0.07
BOD	0.4 (2.4)	0.9 (2.7)	-0.5 (3.6)	-7.6, 6.7	0.90
Q10-1	-0.2 (0.3)	0.3 (0.3)	-0.4 (0.5)	-1.3, 0.5	0.36
Q10-2	-0.1 (0.1)	0.0 (0.0)	-0.1 (0.1)	-0.2, 0.1	0.32

LSM = least square means; H&Y = Hoehn & Yahr; MDS-UPDRS = Movement Disorders Society – Unified Parkinson's Disease Rating Scale; BDI-II = Beck Depression inventory II; BAI = Beck Anxiety Inventory; PDSS-2 = Parkinson's Disease Sleep Scale 2; ESS = Epworth Sleepiness Scale; PDQ-39 SI = Parkinson's Disease Questionnaire 39 Summary Index; MOB = mobility; ADL = activities of daily living; EMO = emotional wellbeing; STI = experienced stigma; SOC = social functioning; COG = cognition; COM = communication; BOD = bodily discomfort; Q10 = Questionnaire for Wearing-Off; CGI = Clinical Global Impression; CGI-S = CGI - Severity Index; CGI-E = CGI - Efficacy Index; CGI-I =CGI - Clinical Global Improvement; n.a. = not applicable

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Safety

In the active group, 91.9%, and in the control group, 88.6% of participants reported to have no subjective experience of side effects on the CGI-E Side Effects question (p = 0.58). AEs are presented in Table 3. Twenty-six participants reported AEs: 18 (40%) in the active and 8 (17%) in the control group (p = 0.02). All AEs were clinically non-significant. Nervous system AEs were most commonly reported, and occurred more frequently in the active (n = 8) than the control group (n = 1, p = 0.01). Nervous system AEs in the active group included paresthesia (n = 1), dizziness (n = 2), nerve compression (n = 1), and headache (n = 1). In the control group, one subject reported dizziness. Ocular events were reported for four subjects in the active group and two in the control group (p = 0.43). The eye exam at the end of treatment was completed by 87 participants. No ocular damage was reported. Two subjects withdrew due to AEs: one participant in the control group who experienced vertigo and one in the active group, who experienced a decreased vision in the left eye.

Table 3: **Adverse events as reported in the Safety population.**

Adverse events (ATC System Organ Class)	**Spectramax LT** *Number (%) of AEs* *n = 45*	**Control** *Number (%) of AEs* *n = 47*	**Fisher's test** **p-value**
Ear and labyrinth disorders	1 (2.2%)	1 (2.1%)	1.00
Eye disorders	4 (8.9%)	2 (4.3%)	0.43
Gastrointestinal disorders	0	2 (4.3%)	0.50
General disorders and administration site conditions	1 (2.2%)	0	0.49
Infections and infestations	3 (6.7%)	1 (2.1%)	0.36
Injury, poisoning, and procedural complications	4 (8.9%)	3 (6.4%)	0.71
Investigations	1 (2.2%)	0	0.49
Musculoskeletal and connective tissue disorders	1 (2.2%)	2 (4.3%)	1.00
Neoplasms (benign, malignant, and unspecifie, including cysts and polyps)	1 (2.2%)	0	0.49
Nervous system disorders	8 (18.0%)	1 (2.1%)	**0.01**
Psychiatric disorders	1 (2.2%)	0	0.49
Renal and urinary disorders	0	1 (2.1%)	1.00
Surgical and medical procedures	1 (2.2%)	1 (2.1%)	1.00
Total	18 (40.0%)	8 (17.0%)	**0.02**

Four Serious AEs (SAEs) were reported during the trial. In the active group, one participant was hit by a car while on the sidewalk, one fell and broke ribs, and one experienced a transient ischemic attack. In the control group, one participant required hip surgery. None were considered to be related to treatment. Eight Device Deficiencies were reported, seven in the Spectramax LT and one in the control group. In each case the device stopped working for mechanical reasons and did not present a safety risk.

Discussion

In this clinical trial, we examined the safety and efficacy of the Spectramax LT device, which emits narrow band blue/green light therapy, as compared to a control light device emitting broad bandwidth polychromatic light. Blue light has proved to be more effective than white light in the suppression of melatonin secretion, shift of circadian rhythms and increase of alertness (21, 22). PD patients, however, may be less sensitive to blue light than healthy individuals (23), and early pilot data suggest that green light may have beneficial effects on motor symptoms. The Spectramax LT device was therefore designed to emit narrow band blue/green light. As far as we are aware, this is the first RCT to investigate the safety and efficacy this type of LT in a PD population.

There were no significant between-group differences in PD severity as measured with the original primary outcome (MDS-UPDRS Part II + III), but the revised primary outcome (MDS-UPDRS Part I + II+III) almost reached significance. The treatment effect and changes from baseline were of a clinically meaningful magnitude, but effects on Part I were larger than on Part II and Part III. Since the MDS-UPDRS primarily measures motor performance, and dopaminergic therapies mainly affect motor symptoms, measuring patients in the ON state may have resulted underestimation of the improvement. Moreover, our study sample was relatively mildly affected at baseline (with mean H&Y stage 2 at baseline), and Spectramax LT treatment effects might be larger in more advanced disease stage. The significant improvements seen in PD-related quality of life (PDQ-39) and clinical impression of global improvement (CGI-I) reflect a clinically meaningful difference. The strongest statistical effects were seen on MDS-UPDRS Part I score. This is of clinical importance, as non-motor manifestations of PD are common and have limited treatment options (24). Our finding is supported by other PD light therapy trials (5-7, 25-27), all of which have shown improvement in non-motor symptoms. Paus et al. (2007) found improvements in mood (6). Rutten et al. (2018) showed improvements in subjective sleep quality (26). Videnovic et al. (2017) found improvement in subjective sleep measures and excessive daytime sleepiness, consistent with the trend on the ESS in this study (5). As LT exerts its effects through an influence on the circadian system (10), the non-motor effects from these studies differ from the effects seen with dopaminergic therapy.

All studies reported to date found beneficial effects of LT on both motor and non-motor manifestations of PD, without significant side effects (5-7, 25-27). In this study, LT was generally well tolerated. AEs were more common in the active treatment group, but were not clinically significant, and no SAEs were related to the intervention. Participants' dropout rate was only 10%, with a majority in the Spectramax LT group.

In summary, Spectramax LT was well tolerated among participants with PD, resulting in improvement of health-related quality of life and non-motor manifestations of PD, with the the improvement in PD symptom severity failing to reach significance. When administering LT, duration, frequency, timing, and its spectral properties need to be considered. Further systematic investigations of LT in PD are needed to define optimal dosing for use in this population, and these variables may vary depending on symptoms that are being targeted. The results of this RCT supports the scientific foundation for considering LT as a promising treatment option for PD patients. Larger double-blind studies are, however, warranted to further study the effectiveness of this type of LT in PD.

Supplementary material

Sample size calculation

The sample size calculation for this study was based on an open label study comparing the effect of bright light therapy in PD patients by Willis et al. (2012) (11). Table S1 shows the minimum number of subjects (n) required to demonstrate an effect on various motor and non-motor symptoms of PD after five months of BLT.

***Table S1*: Minimal sample size required for 80% power using a two-sided alpha of 0.05.**

	Bradykinesia	Rigidity	Tremor	FTE Latency	FTK Latency	Depression	Anxiety	Insomnia
μ1	2.0	1.8	1.7	17	16	1.7	2	1.6
μ2	1.0	0.9	1.0	12	12	0.5	1	0.8
SD	1.4	1.1	1.1	9	4	1.2	1.2	0.8
CV	1.4	1.6	1.5	1.9	4.0	1.4	1.7	2.0
% effect	50	50	59	71	75	29	50	50
n =	23	18	29	38	12	17	24	17

FTE = fist-to-elbow timed motor test; FTK = foot-to-knee timed motor test; μ1 = estimate for the control group; μ2 = estimate for the experimental group; SD = Standard Deviation, CV = coefficient of variation

The average percentage treatment effect across these eight items was a 54% reduction from the control group change (experimental group mean = 46% of control group mean). The average coefficient of variation (CV = SD / mean) for the control group across these eight items was 0.57. For this average percentage treatment effect, the sample size required for 80% power for a two-sided test at alpha = 0.05 with a 54% reduction from control group change and a CV of 0.57, is 19 subjects per treatment group.

However, since this average treatment effect was only a crude approximation of the primary efficacy endpoint, and since the sample sizes for the individual eight parameters ranged from 12 to 38 at five months, a more conservative sample size estimate of 40 patients per group was chosen.

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8

Chapter 8

A double-blind randomized controlled trial to assess the effect of bright light therapy on depression in patients with Parkinson's disease

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Abstract

Background

A disturbed circadian rhythm seems to be a causal factor in the occurrence of depressive disorders in patients with Parkinson's disease (PD). The circadian rhythm can be restored with light. Therefore, Bright Light Therapy (BLT) might be a new treatment option for depression in PD patients.

Methods / design

In this double-blind controlled trial, 84 subjects with idiopathic PD are randomized to either BLT or a control light condition. The BLT condition emits white light with an intensity of 10,000 Lux, while the control device emits dim white light of 200 Lux, which is presumed to be too low to influence the circadian rhythm. Subjects receive 30 minutes of home treatment twice daily for three months. Timing of treatment is based on the individual chronotype. After finishing treatment, subjects enter a follow-up period of six months. The primary outcome of the study is the severity of depressive symptoms, as measured with the Hamilton Depression Rating Scale. Secondary outcomes are alternative depression measures, objective and subjective sleep measures, and salivary melatonin and cortisol concentrations. For exploratory purposes, we also assess the effects on motor symptoms, global cognitive function, comorbid psychiatric disorders, quality of life and caregiver burden. Data will be analyzed using a linear mixed models analysis.

Discussion

Performing a placebo-controlled trial on the effects of BLT in PD patients is challenging, as the appearance of the light may provide clues on the treatment condition. Moreover, fixed treatment times lead to an improved sleep-wake rhythm, which also influences the circadian system. With our study design, we do not compare BLT to placebo treatment, i.e. an ineffective control treatment. Rather, we compare structuring of the sleep-wake cycle in both conditions with additional BLT in the experimental condition, and additional dim light in the control condition. Participants are not informed about the exact details of the two light devices and the expected therapeutic effect, and expectancies are rated prior to the start of treatment. Ideally, the design of a future study on BLT should include two extra treatment arms where BLT and control light are administered at random times.

Trial registration

This trial was registered on ClinicalTrials.gov on May 17th 2012 (ClinicalTrials.gov Identifier: NCT01604876).

Background

In patients with Parkinson's disease (PD), clinically relevant symptoms of depression occur in up to 35%, with approximately 17% fulfilling criteria for major depressive disorder (MDD) (1). Depression has a major impact on overall functioning: depressed PD patients score lower on scales assessing activities of daily living, show a more rapid deterioration of motor and cognitive functioning, and have a higher mortality (2-4). Depression is highly correlated with insomnia in PD (5-7), both contributing to a reduced quality of life in PD patients and their caregivers (3, 5).

Current treatment options for depression in PD are limited. Antidepressants can have side effects, such as orthostatic hypotension, sedation, and anticholinergic adverse effects, and may aggravate motor symptoms (8-10). Cognitive behavioral therapy might be effective for the treatment of depression in PD patients, but has not been extensively studied yet (11). To date, there are no evidence-based treatment options for insomnia in PD, and treatment with hypnotics can have adverse effects (7). For patients with cognitive dysfunctions, which are common in PD (12), psychotherapy is not always a feasible treatment option. An alternative treatment for depressive disorders and insomnia in PD patients is therefore needed.

Involvement of the circadian system in depression in PD

The circadian rhythm consists of neuroendocrine and behavioral cycles of approximately 24 hours. This rhythm is generated by the 'biological clock', the suprachiasmatic nucleus (SCN), which is located in the hypothalamus (13). The SCN promotes wakefulness during the day and sleep during the night, providing the body with a pattern of rest and activity that corresponds to the day-night cycle. Moreover, the SCN is involved in mood regulation through the influence on neurotransmitter systems (14).

The circadian system regulates the secretion of several hormones, including melatonin and cortisol (15). Under normal circumstances, the pineal gland starts secreting melatonin two to three hours prior to bedtime to promote sleep (15). When plasma or saliva samples are taken under dim light conditions, this rise in melatonin levels is referred to as the dim-light melatonin offset (DLMO) (16). In the morning, the secretion of melatonin is inhibited by exposure to light, leading to a decrease in melatonin concentrations (15). Cortisol concentrations, on the other hand, peak in the morning, reflecting the response of the hypothalamic-pituitary-adrenal axis to awakening (15, 17). This peak is referred to as the cortisol awakening response (18). A more indirect measure of the circadian rhythm is the chronotype: the propensity of an individual to be active or asleep during a 24-hour period,

with ‘morning’ and ‘evening types’ at the extremes of the spectrum. The chronotype can be measured with the Morningness – Eveningness Questionnaire (MEQ) (19). Previous studies have shown a significant correlation between the MEQ score and the DLMO (19, 20).
Since the endogenous rhythm of the SCN is slightly different from the societal 24-hour day-night cycle, it has to be entrained by input signals from the environment called ‘zeitgebers’, such as light, physical activity and food intake (13, 21). Disrupting input to the biological clock can lead to a disturbed circadian rhythm, as reflected in a shift or change in amplitude of the cortisol and melatonin secretion patterns. A misalignment of the circadian rhythm is associated with depressive symptoms and insomnia (22-24).

PD patients are prone to desynchronization of the circadian rhythm, due to dopamine deficiency and conflicting input to the SCN (25). Indeed, a disturbed circadian rhythm is observed in this population. Three studies described a phase advance of melatonin secretion in PD subjects (26-28). Moreover, a decrease in the amplitude and total amount of melatonin and cortisol secretion has been observed (29, 30). In another study, the pattern of cortisol secretion was also blunted, but total cortisol concentrations were increased in PD subjects compared to healthy controls (31). These changes in melatonin and cortisol secretion patterns have also been reported in non-PD subjects with a depressive disorder or insomnia (32-34). Based on these findings, we hypothesize that a disturbed circadian rhythm is involved in the pathophysiology of depression and insomnia in PD.

Bright Light Therapy

Light stimulates melanopsin-containing ganglion cells in the retina, providing the SCN with a ‘daytime’ signal via the retinohypothalamic tract (13). Bright Light Therapy (BLT) therefore acts as a strong zeitgeber that can restore circadian rhythmicity. Light exposure in the morning advances the circadian rhythm and is effective in the treatment of depressive disorders (35-39), while evening light delays the rhythm and is thought to be more effective in the treatment of early awakening insomnia (32). Since PD patients have an advanced circadian rhythm (26-28), evening light might be effective in treating not only insomnia, but also depressive symptoms in this population.

In their frequently cited meta-analysis, Golden et al. (2005) concluded that BLT is effective in the treatment of depression in non-PD samples (36). Recent meta-analyses are more cautious in drawing conclusions on the efficacy of BLT due to limitations of the performed studies, e.g. small and heterogeneous study samples, short treatment duration and lack of a proper placebo condition (35, 37, 38). The same issue was raised in a Cochrane review on the effects of BLT for treating insomnia in adults aged 60 years and older (40). However, since treatment effects of pharmacotherapy alone for these disorders are limited, and BLT is a low-cost treatment with a relatively high safety and tolerability (41), it is a treatment option that deserves further research.

In PD, the effects of BLT have been evaluated in two pilot studies (42, 43) and one retrospective, open label study (44). These studies demonstrated positive effects on depressive symptoms, sleep and motor symptoms. However, depression was not the primary outcome measure in all studies, and all studies had methodological limitations. Therefore, further research on the efficacy of BLT in the treatment of PD patients with a depressive disorder is warranted.

Methods

This study aims to investigate whether BLT is more effective in reducing depressive symptoms in patients with PD and a depressive disorder, than a control light device. For secondary research purposes, we assess the effects of BLT on insomnia and circadian rhythmicity.

Study design and procedures

The design of this study is a double-blind randomized controlled clinical trial. An overview of all study procedures is given in Table 1.
After (self-)referral, subjects are sent an information package about the study. If still interested in participation after reading the additional information, prospective participants are screened by telephone by the first assessor (SR, psychiatry resident). When eligible, subjects are invited for an appointment with the first assessor. During this visit, subjects can ask any remaining questions. After providing written informed consent, subjects are randomized to the experimental or control condition by a research coordinator (CV), and baseline clinical assessments are performed. At the end of the visit, subjects are asked to perform actigraphy, keep a sleep diary and wear a light sensor at home for the upcoming seven days. After this week, all baseline assessments are completed and a BLT or control device is installed at the subject's home by the study coordinator or a trained research assistant. After a demonstration of the device, the three-month treatment phase starts. Clinical assessments are repeated halfway (T1) and at the end of treatment (T2). After completing treatment, subjects enter a six-month follow-up phase. Subsequent interventions are allowed within the follow-up phase, since we consider it unethical to withhold treatment from patients with remaining depressive symptoms. Follow-up assessments take place one (T3), three (T4) and six months (T5) after completing treatment.

Prior to each follow-up assessment, subjects receive a package containing questionnaires, a sleep diary, actigraphy watch, light sensor and cotton dental rolls for saliva sampling, to perform these measures at home in the week prior to the assessment visit.

Randomization and blinding

To maintain blinding of the assessors, the research coordinator (CV) performs block randomization. Blocks are generated per season to rule out seasonal influences on the treatment effect. Both subjects and assessors are blinded for the treatment condition. To prevent unblinding, subjects are asked not to share any details of their treatment with their assessor. When patients do reveal their condition, the assessor is immediately replaced by the blinded project's principle investigator (OvdH, psychiatrist).

Participants

Participants for this study are recruited throughout the Netherlands by various strategies, including referral by a neurologist, psychiatrist or other medical professional, recruitment through media of various associations involved with PD, and advertisement in a Dutch national newspaper.

Patients are eligible for inclusion when they are diagnosed with idiopathic PD by a neurologist. In addition, they are required to meet criteria of a major depressive disorder as classified by the DSM-IV (45). Patients with a bipolar disorder are excluded due to the risk of inducing (hypo)mania with BLT (38). We also exclude subjects with a current psychosis, due to the potential influence on our assessments and the risk of noncompliance. Finally, we exclude patients with a (relative) contraindication for BLT, such as a disorder associated with photosensitization reactions to light, e.g. porphyria, macular degeneration, retinal dystrophy, or lupus erythematosus, or when they have used pharmacological agents with a photosensitizing effect within the past four weeks (20). Because changes in the use of antiparkinsonian or psychiatric medication might influence assessments, participants have to be on a stable dose of medication for at least four weeks before inclusion. Moreover, subjects and their physicians are asked not to change the medication regime during the treatment phase of the trial, unless this is deemed medically necessary.

Table 1: **Overview of study procedures.**

	STUDY PERIOD						
	Enrolment and allocation	**Post-allocation**					
Time point →	**T-1**	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**
weeks →	*-1*	*-1 to 0*	*6*	*12*	*16*	*24*	*36*
ENROLMENT:							
Eligibility screen	x						
Informed consent	x						
Allocation	x						
INTERVENTIONS:							
Experimental intervention		----------					
Control intervention		----------					
ASSESSMENTS:							
HDRS		x	x	x	x	x	x
GDS-30		x	x	x	x	x	x
SCOPA-SLEEP		x	x	x	x	x	x
CSD		x	x	x	x	x	x
MEQ		x	x	x	x	x	x
SCID-I		x		x			x
UPDRS-III and -V		x		x			x
MMSE		x		x			x
WHO-QOL		x		x			x
ZBI		x		x			x
CEQ		x					
Actigraphy		x	x	x	x	x	x
Saliva sampling		x	x	x	x	x	x
Environmental light exposure		x	x	x	x	x	x

HDRS = Hamilton Depression Rating Scale; GDS-30 = 30-item Geriatric Depression Scale; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease - Sleep; CSD = Consensus Sleep Diary; MEQ = Morningness-Eveningness Questionnaire; SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders; UPDRS = Unified Parkinson's Disease Rating Scale; MMSE = Mini Mental State Examination; WHO-QOL-BREF = World Health Organization Quality of Life assessment, abbreviated version; ZBI = Zarit Burden Interview; CEQ = Credibility / Expectancy Questionnaire

Intervention

The experimental condition consists of BLT with a Brazil® Lightbox (Lumie, Cambridge, United Kingdom). This BLT device emits white, broad spectrum light. During treatment sessions, subjects are instructed to take place in front of the device at a distance of 30 centimetres, at which the intensity of the light is 10,000 Lux. To create a credible control condition, neutral density filters (Lee Filters, type 209.03ND, Hampshire, United Kingdom) are installed in the light device, so that the experimental and control device have an identical appearance when switched off. These filters reduce transmission uniformly, giving the light a dim white appearance. Subjects are instructed to position themselves at a distance of 40 centimeters from the control device, at which the light intensity is approximately 200 Lux. At this light intensity, which is lower than in a dimly lit room, no substantial effect on circadian rhythmicity is expected (46).

Subjects in both conditions follow the treatment at home for a period of three months. Subjects use the device both in the morning and the evening. Treatment duration per session is 30 minutes, which is sufficient to entrain the SCN at an intensity of 10,000 Lux (20). Timing of the morning treatment session is based on the score on the MEQ (19, 41). Since evening BLT should be administered at least 90 minutes prior to bedtime (20), the evening session takes place 9,5 hours prior to the morning BLT, in order to allow eight hours of night-time sleep. To increase user convenience and compliance, the device is attached to a timer, so that the device switches on automatically at the times set for treatment.

Outcomes

Primary outcome measure

The primary outcome measure of this study is the change in depressive symptoms as regards to baseline, as measured with the 17-item version of the Hamilton Depression Rating Scale (HDRS) (47), from baseline (T0) to the end of treatment (T2).

Secondary outcome measures

Our secondary outcome measures are (1) alternative depression measures, (2) subjective and objective quality of sleep, and (3) circadian rhythmicity. Since we are mainly interested in the direct and long-term treatment effects, all outcome measures described below concern the difference between the treatment groups in the change in outcome measures as regards to the baseline value between i) baseline and the end of treatment (T0 to T2) and ii) baseline and the end of follow-up (T0 to T5).

1. Additional depression measures:
   The change in HDRS-score between T0 and T5 is considered as a secondary outcome measure. As an alternative measure for depression, we use the Geriatric Depression Scale (GDS-30) (48), a self-report instrument. The GDS-30 does not contain items regarding somatic symptoms of depression, and might therefore have a higher diagnostic specificity in PD (48). As a third depression measure, we assess the proportion of subjects in each treatment group that achieves complete remission at T2 and T5, i.e. fulfilling DSM-IV criteria of a 'depressive disorder in full remission', as determined with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (49).

2. Sleep:
   a. Subjective experience of sleep is measured with the Scales for Outcomes in Parkinson's Disease-Sleep (SCOPA-SLEEP) (50), a validated self-report instrument that contains two subscales: one rating night-time sleep disturbances and one on excessive daytime sleepiness. Both subscale scores are used as a secondary outcome measure.
   b. Sleep patterns are objectified by actigraphy, which is considered to be a valid alternative for polysomnography in the quantitative evaluation of sleep in PD patients (51). Subjects are asked to wear an actigraphy device (GENEActiv Sleep; GENEActiv, Huntingdon, United Kingdom) on their non-dominant wrist continuously for seven consecutive days. Sleep parameters are calculated in two steps. First, accelerometry data is preprocessed with GENEActive PC software version 2.2, using reports of time of attempted sleep and time of final awakening from the Consensus Sleep Diary (CSD) (52). Second, the raw GENEActive accelerometry data are converted into Actiwatch counts, as described by Te Lindert et al. (2013), to calculate sleep parameters. The sleep parameters of main interest are total sleep time and sleep fragmentation, i.e. the number of wake bouts per night.

3. Circadian rhythmicity:

   In this study, we use salivary concentrations of melatonin and cortisol as markers for the circadian rhythm. At each time point in the study, subjects are instructed to collect saliva at home during a single day, using cotton dental rolls (Salivette®, Sarstedt, Numbrech, Germany). The first saliva sample is taken immediately after waking up, followed by three more samples at an interval of 30 minutes. In the evening, subjects start hourly collection of samples four hours prior to intended bedtime. Samples are preserved in the refrigerator by the patient, and collected by the researchers one or two days later. They are centrifuged and stored at -80 °C until all samples of one subject that are collected throughout the study can be analyzed simultaneously.

   The cortisol concentration in the saliva samples is determined by on-line solid-phase extraction liquid chromatography tandem mass spectrometry (XLS-MS/MS), which is preferred over immunoassays to prevent cross-reactivity with other corticosteroids (53). We will calculate the area under the curve with respect to the ground (AUC_G) and the area under the curve with respect to the index of salivary cortisol change over time (AUC_I), as described by Pruessner et al. (2003) (54). The AUC_G is an estimate of the total cortisol secretion throughout the day, whereas the AUC_I is a measure of the cortisol awakening response. The AUC_G and AUC_I of the salivary cortisol concentrations of the morning samples are considered as a secondary outcome measure. We will also report the cortisol concentration in the

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first saliva sample taken as a measure of the endpoint of pre-awakening increase in cortisol (17).

The melatonin concentrations are assessed in the evening saliva samples using liquid chromatography tandem mass spectrometry (LS-MS/MS). We will calculate the DLMO with the 'hockey-stick method', as described by Danilenko et al. (2013) (55).

Assessments for exploratory purposes

For exploratory purposes, we assess the difference between the treatment groups in the absolute change in the following outcome measure from T0 to T2 and T0 to T5.

1. Subjective quality of sleep, rated in the CSD on a scale ranging from 0 (very poor) to 4 (very good).
2. Sleep efficiency as objectified with actigraphy. Sleep efficiency is defined as the percentage of time the subject spent asleep between onset of sleep and getting up in the morning.
3. Evening cortisol secretion, calculated as both the AUC_G and $AUC_{I.}$
4. Global cognitive function, assessed with the Mini Mental State Examination (MMSE) (56).
5. Presence of comorbid psychiatric disorders, as determined with the SCID-I.
6. Severity of motor symptoms, using section III of the Unified Parkinson's Disease Rating Scale (UPDRS) (57). The UPDRS-III is rated by the first assessor, who is trained by a movement disorder specialist (HB).
7. The chronotype, as determined with the MEQ.
8. Quality of life, as measured with the abbreviated version of the World Health Organization Quality of Life assessment (WHOQOL-BREF) (58).
9. Caregiver burden, as reported by the caregiver on the Zarit Burden Interview (ZBI) (59).

Covariates

In order to control for factors that might influence the association between treatment and the outcome measures, we collect the following additional data:

1. Medication use:

   Current medication use is reviewed at each assessment. Since dopaminergic agents can have a positive influence on mood in PD patients with depressive symptoms (60), we will control for the total dose of dopaminomimetics, which is converted to a levodopa equivalent daily dose using the conversion rate described by Olde Dubbelink et al. (2013) (61). Moreover, we will correct for the initiation or change in dosage of antidepressants or sleep medication.

2. Exposure to environmental light:
   We collect data on the exposure to environmental light using a light sensor (Actiwatch Light®, Cambridge Neurotechnology Ltd., Cambridge UK). Subjects are asked to continuously wear the sensor on the outer layer of their clothing for seven consecutive days. Raw data on light exposure is pre-processed with Actiwatch Activity & Sleep Analysis 5 software, after which total amount of light exposure during the day is calculated using custom-made in-house software.

3. Expectancy:
   In a previous study on BLT, a positive correlation between expectations and treatment response was found (62). In this study, we assess the expectancies of our subjects with the Credibility / Expectancy Questionnaire (CEQ) (63), after installation of the device at home.

4. Compliance:
   Compliance with treatment is assessed with an occupancy data logger (HOBO® occupancy/light logger) that is attached to the device. The logger detects the time and duration of presence of the participant in front of the device. Treatment session compliance is defined as exposure to the device for at least 70% of the prescribed duration, i.e. 21 out of 30 minutes, within the set time frame. Total compliance is calculated as the proportion of sessions that a subject is compliant with therapy. We assess the effects of total compliance on the intervention effect, as well as compliance with morning and evening therapy separately.

Side effects and treatment satisfaction

Prior to the start of the trial, we made an overview of potential adverse effects that subjects might experience during treatment, based on previous reports (41, 64). One week after the start of treatment, subjects are contacted by telephone by the research assistant to inquire about these side effects. At assessment visit T1, patients are also screened for side effects. We will report the difference in prevalence of reported side effects between both groups.

After completing the treatment phase, all patients are asked to rate their appreciation of timing and duration of therapy sessions on a visual analogue scale (VAS). Moreover, they indicate on a VAS the extent to which they would like to continue treatment after the end of the trial. We will report average VAS scores as an indicator of treatment satisfaction per group.

Statistical analysis

Sample size calculation

Prior to the start of the study, we calculated the necessary sample size for a sufficient power at the end of treatment (T2) in a mixed models analysis. We aimed to have sufficient sensitivity for a minimal standardized effect size of Cohen's $d = 0.6$, with an estimated standard deviation of 1.0 and intra-subject correlation of assessments of $\rho = 0.6$. For a statistical power of 80% and a two-tailed significance level of $p < 0.05$, 35 subjects per treatment group were required. To correct for a maximum drop-out of 20%, we would need 7 additional subjects per group, resulting in a total sample size of 84 subjects.

Efficacy analysis

Analyses will be performed on the Modified-Intent-To-Treat population, which consists of all subjects randomized in the trial who received at least one week of light treatment and provided at least one post-baseline assessment of the HDRS. As a sensitivity analysis, we will compare the baseline characteristics to the Intent-to-Treat population, i.e. all subjects who were randomized in the trial. To assess the effect of treatment duration, we will also assess the effects in the Per Protocol-population, i.e. all subjects who completed the three months treatment duration.

Demographics and clinical characteristics of both the BLT and control group at baseline will be presented with percentages or mean scores with standard deviations. Correlations between continuous variables at baseline will be calculated using Pearson's correlation coefficients.

The effect of the intervention on the change from T0 to T2, and from T0 to T5, in outcome measures will be assessed using a linear mixed-effects model analysis with assessment visit as the lowest level, and patient as highest level. Time of assessment will be handled as a categorical variable. The effect of the intervention on the outcome measures over time will be modelled by an intervention by time interaction with two degrees of freedom. In all analyses, we will correct for baseline values of the outcome variable. In addition, we will assess whether adding the covariates to the regression model leads to a significant change of the regression coefficient of the condition effect of ≥ 10%.

No imputation of missing values will be performed, since linear mixed models handle missing data by placing the data in long format, where the available data of each measurement is nested within persons.

Discussion

Performing a placebo-controlled trial on the effects of BLT is challenging, since the appearance of the device or the characteristics of the emitted light can provide the subject with clues about the treatment condition. This can influence the subject's expectancies of the treatment, which has been shown to impact on the outcomes of a study on BLT the past (62). Deactivated negative ionizers, dim red light and light boxes with full-band filters were used as control light conditions for BLT in previous studies (37, 65). In this trial, we also use a light device with full-band filter. However, the reduced intensity of the light could point out that the subjects in the control condition were not receiving BLT. Therefore, subjects' expectancies are rated prior to the start of treatment, and participants are not informed about the exact details of the two light devices and their expected therapeutic effect. Although this might raise ethical questions, it is a valid way to guarantee subject blinding when studying a treatment that lacks a credible placebo condition. Therefore, this study did receive approval of the ethics committee. Moreover, the subjects in the control condition do receive some form of treatment. All subjects in our study are required to use the light device at fixed times in the morning and the evening, imposing a fixed sleep-wake structure on all participants. According to the 'social zeitgeber hypothesis' of Ehlers et al. (1988), a disruption of social rhythms can induce a depressive episode through disturbance of the circadian rhythm (66). Restoring the circadian rhythm by re-establishing daily routines, including time of awakening and going to bed, might therefore have a positive influence on mood (66). Since all participating subjects in our study achieve a more regular sleep-wake cycle, we feel that subjects in the control condition are not completely deprived of treatment. Moreover, a report by Zeiter et al. (2000) suggests that dim light of approximately 100 lux also has the ability to cause a shift in circadian rhythm (67). Although the healthy volunteers participating in this study were exposed to the light for 6.5 hours (67), we cannot rule out the possibility that 30 minutes of exposure to 200 lux of light will influence the circadian system of PD patients.

With our study design, we do not compare BLT to 'pure' placebo treatment, i.e. an ineffective control treatment. Rather, we compare structuring of the sleep-wake cycle through set treatment times in both conditions, with additional BLT in the experimental condition, and additional dim light in the control condition. In order to be able to assess the effects of BLT only, a future study on the effects of BLT on depression in PD would have two additional treatment arms, where BLT and control light are administered at random times. Moreover, more research is needed on the timing (morning or evening) and duration of BLT, as well as the influence of light intensity. However, we hypothesize that with the design of this study, we will still find a greater improvement on depression, insomnia and biomarkers of circadian rhythmicity in the subjects in our experimental condition as compared to our control subjects, due to the addition of BLT to the imposed sleep-wake structure.

List of abbreviations

AUC_G = area under the curve with respect to the ground; AUC_I = area under the curve with respect to the index of salivary cortisol change over time; BLT = Bright Light Therapy; CAR = cortisol awakening response; CEQ = Credibility / Expectancy Questionnaire; CSD = Consensus Sleep Diary; DLMO = dim-light melatonin onset; DSM-IV= Diagnostic Statistical Manual, fourth edition; GDS-30 = 30-item Geriatric Depression Scale; HDRS = Hamilton Depression Rating Scale; LS-MS/MS = liquid chromatography tandem mass spectrometry; MDD = major depressive disorder; MEQ = Morningness-Eveningness Questionnaire; MMSE = Mini Mental State Examination; PD = Parkinson's disease; RCT = randomized controlled trial; SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders; SCN = suprachiasmatic nucleus; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease - Sleep; UPDRS = Unified Parkinson's Disease Rating Scale; WHO-QOL-BREF = World Health Organization Quality of Life assessment, abbreviated version; XLS-MS/MS = on-line solid-phase extraction liquid chromatography tandem mass spectrometry; ZBI = Zarit Burden Interview

Ethics approval and consent to participate

This study was approved by the ethic committee of the VU University medical center (VUmc; study number 2012/75). All subjects provide written informed consent before inclusion. Quality and safety of the study, as described in the Good Clinical Practice Guidelines (GCP), was guaranteed through monitoring by the Clinical Research Board of the VUmc and GCP training of all researchers.

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9

Chapter 9

Bright light therapy for depression in Parkinson's disease: a randomized controlled trial

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Abstract

Objective

To assess the efficacy of Bright Light Therapy (BLT) in reducing depressive symptoms in patients with Parkinson's disease (PD) and major depressive disorder (MDD), compared to a control light.

Methods

In this double-blind controlled trial, we randomized patients with PD and MDD to treatment with BLT (± 10,000 Lux) or a control light (± 200 Lux). Participants were treated for three months, followed by a six-month naturalistic follow-up. The primary outcome of the study was the Hamilton Depression Rating Scale (HDRS). Secondary outcomes were objective and subjective sleep measures and salivary melatonin and cortisol concentrations. Assessments were repeated halfway and at the end of treatment, and one, three and six months post-treatment. Data were analyzed using a linear mixed models analysis.

Results

We enrolled 83 participants. HDRS scores decreased in both groups, without a significant between-group difference at the end of treatment. Subjective sleep quality improved in both groups, with a larger improvement in the BLT group (B (SE) = 0.32 (0.16), $p = 0.04$). Total salivary cortisol secretion decreased in the BLT group, while it increased in the control group (B (SE) = -8.11 (3.93), $p = 0.04$).

Conclusions

BLT was not more effective in reducing depressive symptoms than a control light. Mood and subjective sleep improved in both groups. BLT was more effective in improving subjective sleep quality than control light, possibly through a BLT-induced decrease in cortisol levels.

Classification of evidence

This study provides Class I evidence that BLT is not superior to a control light device in reducing depressive symptoms in PD patients with MDD.

Introduction

The prevalence of major depressive disorder (MDD) in patients with Parkinson's disease (PD) is 17%, and insomnia occurs in at least 30% (1, 2). Both are associated with a reduced quality of life and poorer daytime functioning (1-5). A disturbed circadian rhythm may contribute to the development of depression and insomnia in PD patients (6, 7). Bright Light Therapy (BLT) can positively influence sleep and mood by supporting the circadian pacemaker, and may therefore be an alternative treatment option for depression and insomnia in PD (8, 9). Previous studies on the effects of BLT demonstrate a positive effect on mood, sleep, excessive daytime sleepiness (EDS) and motor symptoms (10-13). To date, however, no study used a randomized-controlled trial (RCT) design to evaluate the effect of BLT on depression in PD. In this RCT, we investigated the hypothesis that BLT is more effective in reducing depressive symptoms in patients with PD and MDD, than exposure to a control light. Secondary outcomes were objective and subjective sleep parameters and the circadian rhythm markers melatonin and cortisol.

Methods

The primary research question of this study, providing Class I evidence, was: Is BLT more in reducing depressive symptoms, as measured with the Hamilton Depression Rating Scale (HDRS), in PD patients with MDD, than a control light device?

Standard protocol approvals, registrations, and patient consents

This study protocol was approved by the medical ethical committee of the VU University Medical Center. The trial was registered on ClinicalTrials.gov on May 17th 2012 (ClinicalTrials.gov Identifier: NCT01604876, url: https://clinicaltrials.gov/ct2/show/NCT01604876). All participants provided written informed consent.

Study design and procedures

The study protocol of this double-blind RCT was described in detail previously (14).
After providing informed consent, participants were enrolled by the assessor (SR) and randomized to the intervention or control condition by a research coordinator (CV). Block-randomization was performed per season using a computer-generated random number list (in Excel 2007), to rule out seasonal influences on the treatment effect. The randomization list was managed by the research coordinator. The research coordinator

assigned the treatment to a new participant after inclusion by sequentially following the randomization list. Subsequent treatment allocations were therefore not influenced by the previous, and coding of participants did not contain any information about the treatment allocation. This list was stored on a secure and password protected drive separate from all other data, and was not available to the rest of the research team. Both participants and assessors (SR, OvdH) were blinded for the treatment condition. Since the appearance of the device or the characteristics of the emitted light might provide our participants with clues about the treatment condition and influence study outcomes, we did not inform our study participants about the exact details of the two light devices and the expected therapeutic effect. Assessments took place at home, as well as in the research facility and outpatient clinic of the VU University Medical Center. After completion of the baseline (T0) assessments, subjects were asked to keep a sleep diary and to wear a light sensor and actigraphy watch for the subsequent seven days. Moreover, they were asked to collect saliva samples at home in the morning and evening on six days during their participation in the trial: the day prior to the start of treatment (T0), and one day prior to each follow-up assessment. The first sample was taken immediately after waking up, followed by three more at an interval of 30 minutes. In the evening, samples were collected hourly, starting three hours prior to the intended bedtime. After this, a BLT or control light was installed at the subject's home by the research coordinator or a trained research assistant. Participants were treated at home for three consecutive months, after which they entered a six-month naturalistic follow-up. Assessments were repeated halfway (T1) and at the end (T2) of treatment, and one (T3), three (T4) and six months (T5) post-treatment. Prior to each post-baseline assessment (T1-T5), participants received a package containing questionnaires, a sleep diary, actigraphy watch, light sensor and cotton dental rolls for saliva sampling, to perform these measures at home in the week prior to the assessment visit.

Participants

Study participants were recruited throughout The Netherlands using various strategies, including referral by medical professionals, recruitment through various PD-related organizations, and an advertisement in a Dutch national newspaper. The trial ran between July 2012 and January 2017.

Patients diagnosed with idiopathic PD by a neurologist, and meeting MDD criteria according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) (15), were eligible for inclusion. Exclusion criteria were a current psychosis or (relative) contraindication for BLT, such as a bipolar disorder or increased risk of photosensitization due to medication use or a medical disorder (16, 17). Participants had to be on a stable dose of antiparkinsonian and psychopharmacological agents for at least four weeks before inclusion, and were asked not to change the medication regime during the intervention period, unless this was deemed medically necessary.

Intervention

The intervention consisted of BLT with a Brazil® Lightbox (Lumie, Cambridge, United Kingdom), which emits daylight spectrum light with an intensity of 10,000 Lux at a 30 to 40 centimeter distance. For the control condition, neutral density filters (Lee Filters, type 209.03ND, Hampshire, United Kingdom) were installed in the light device, reducing the transmission to 200 Lux. At this light intensity, no substantial effect on circadian rhythmicity was expected (18). Participants were treated at home daily, for 30 minutes in the morning and evening, for three consecutive months. Timing of the morning treatment was based on the score on the Morningness-Eveningness Questionnaire (MEQ), as recommended by the Center for Environmental Therapeutics (see table in 'AutoMEQ' on www.cet.org), within a time frame of 6:00 and 8:15 AM (19, 20). The evening session took place 9.5 hours prior to the morning BLT, in order to allow eight hours of nighttime sleep.

Outcome measures

Primary outcome

The primary outcome measure of this study was the severity of depression at T2, as measured with the 17-item version of the Hamilton Depression Rating Scale (HDRS) (21).

Secondary outcomes

- The total score on the Geriatric Depression Scale (GDS-30) (22).
- The proportion of participants in each treatment group that fulfilled the DSM-IV criteria for a 'depressive disorder in full remission'(15).
- Subjective quality of sleep, as measured with the Scales for Outcomes in Parkinson's Disease-Sleep (SCOPA-SLEEP) (23). Both total score and the scores on the subscales rating daytime sleepiness, nighttime sleep and subjective sleep quality were used.
- Actigraphic estimates of total sleep time and sleep fragmentation, i.e. the number of wake bouts per hour (GENEActiv Sleep; GENEActiv, Huntingdon, United Kingdom).
- Circadian rhythm markers, derived from salivary concentrations of melatonin and cortisol. Using the cortisol concentrations in the morning, we calculated the area under the curve with respect to the ground (AUC_G) and the area under the curve with respect to the index of salivary cortisol change over time (AUC_I) (2003) (24). The morning AUC_G is an estimate of the total cortisol secretion throughout the day, whereas the AUC_I is a

measure of the cortisol awakening response. Melatonin concentrations were used to calculate the dim-light melatonin onset (DLMO) with the 'hockey-stick method' (25).

Exploratory outcomes

- Subjective quality of sleep, rated in the Consensus Sleep Diary (CSD) (26).
- Actigraphic estimation of sleep efficiency, defined as the percentage of time spent asleep between going to bed and getting up in the morning.
- Evening cortisol secretion, calculated as both the AUC_G and $AUC_{I.}$
- Global cognitive function, assessed with the Mini Mental State Examination (MMSE) (27).
- Motor symptoms, assessed with Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (28).
- The score on the MEQ (19).
- The score on the World Health Organization Quality of Life assessment (WHOQOL-BREF) (29).
- Caregiver burden, assessed with the Zarit Burden Interview (ZBI) (30).

Confounding factors

In order to control for factors that might influence the association between treatment and the outcome measures, we corrected our analyses for age, treatment expectancy, as measured with the Credibility/Expectancy Questionnaire (CEQ) (31), compliance with treatment, measured with an occupancy data logger (HOBO® occupancy/light logger, Onset Computer Corporation, Bourne (MA), USA), exposure to environmental light, assessed with a light sensor (Actiwatch Light®, Cambridge Neurotechnology Ltd., Cambridge, UK), dosage of dopaminergic medication converted to the levodopa equivalent daily dose (LEDD) (32), and the use of antidepressants and hypnotic/anxiolytic medications.

Tolerability and safety

Participants were screened for possible adverse effects, based on previous reports, after six weeks of treatment (20, 33). After treatment, all participants were asked to rate their appreciation of the therapy on a 0 - 100 visual analogue scale (VAS).

Statistical analysis

Sample size calculation

We calculated the necessary sample size for a mixed model analysis (34), aiming at sufficient sensitivity for a minimal standardized effect size of Cohen's d = 0.6 and intra-participant correlation of assessments of rho = 0.6. For a statistical power of 80% and a two-tailed significance level of $p < 0.05$, we required 35 participants per treatment group.

To correct for a maximum drop-out rate of 1 out of 6 (16.7%), we would need seven additional participants per group, resulting in a total sample size of 84 participants.

Efficacy analysis

Analyses were performed on the Modified-Intent-To-Treat (mITT) population, consisting of all participants who received at least one week of treatment and provided at least one post-baseline assessment of the HDRS. Linear mixed model analyses were used to analyze the effect of the intervention on the different outcome variables. Mixed model analyses were used to adjust for the dependency of the repeated observations within the patient. The linear mixed models included the intervention variable, time (treated as a categorical variable and represented by dummy variables), the interaction between the intervention and time, and the baseline value of the particular outcome variable. With this model we estimated the differences between the groups at T2 (end of treatment) and T5 (end of study). Due to the adjustment for the baseline value of the particular outcome variable, the differences between the groups at T2 and T5 are equal to the differences in the changes in the outcome between baseline and T2 and between baseline and T5. For all analyses, both crude and adjusted results, adjusted for all potential confounders, were estimated.

Statistical significance was defined as a p-value < 0.05. All statistical analyses were performed with IBM SPSS Statistics 22.

Results

Participants

The trial ran between July 2012 and January 2017. For a flow chart of the study, see Figure 1. Of the 389 patients assessed for eligibility, 306 were excluded, resulting in a sample size of 83. Three participants withdrew prior to randomization, and another eight within the first week of treatment, resulting in a mITT population of 72 participants.

Table 1 demonstrates the descriptives of the mITT population at baseline. Mean age was 64.4 [9.2] SD years, and 44% of the study participants were female. The majority of participants (58%) was in Hoehn & Yahr stage 2. Mean HDRS score was 14.6 [3.6], indicating that most study participants had a moderately severe depression.

Due to an error in the salivary melatonin concentration measurement, analyses on the DLMO could not be performed. Since the assay used to determine the salivary cortisol concentration had a minimum detection limit of 2.0 pg/ml, some of the concentrations were non-detectable. We imputed these with a value of 1.9 pg/ml. Because the number of cortisol concentrations in the evening was considered too low to calculate a reliable AUC_I and AUC_G, we instead calculated the mean evening cortisol concentration, using the salivary cortisol concentration at bedtime, and one and two hours prior to bedtime.

Figure 1: **Flow chart.**

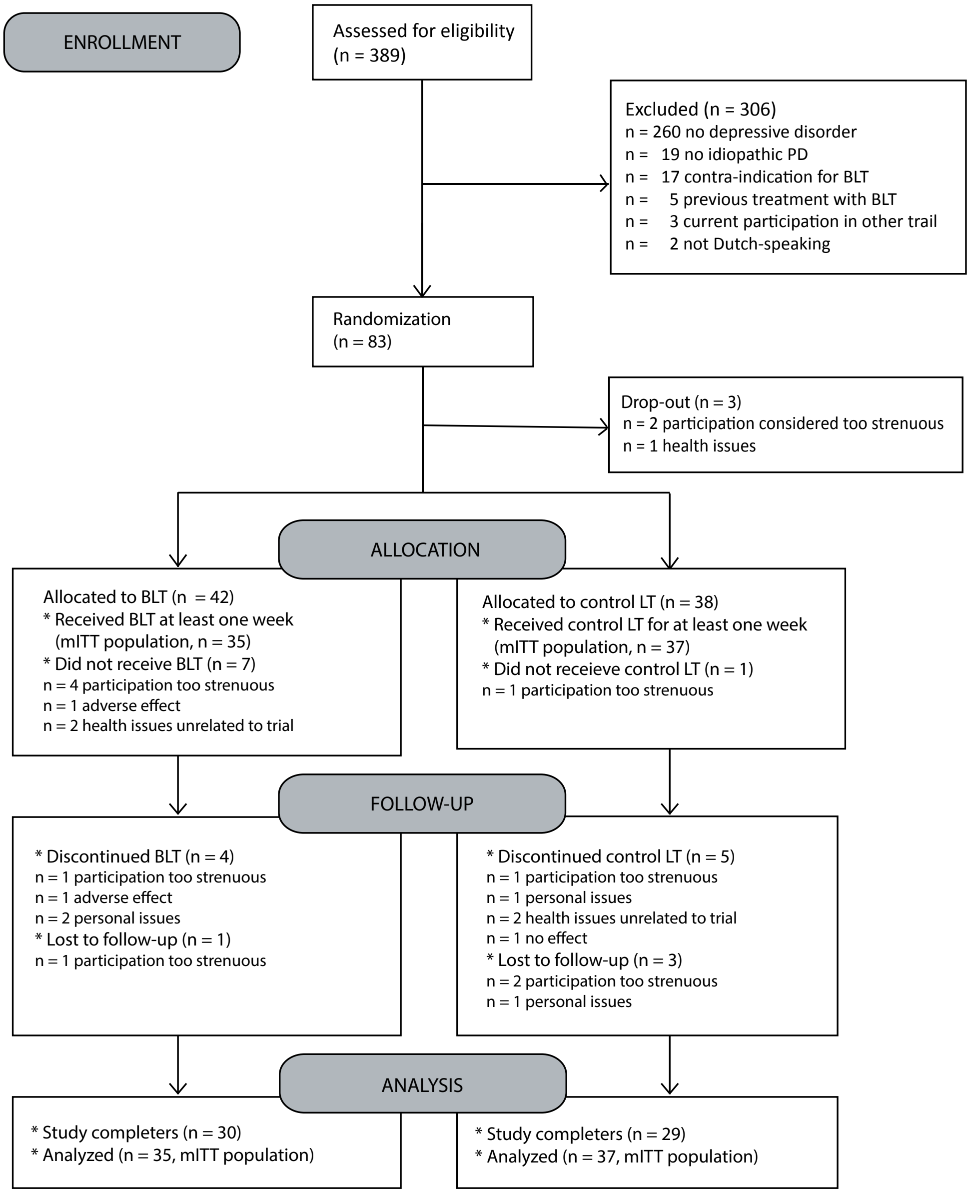

Table 1: **Demographical and clinical characteristics of the mITT population at baseline.**

Variable	Control group			Intervention group		
	n	Mean [SD]	Range	n	Mean [SD]	Range
Age*	37	65.8 [8.6]	[46.3, 82.7]	35	58.9 [8.5]	[36.3, 83.8]
% female (n)	37	46 (17)		35	43 (15)	
% use of antidepressants (n)	37	18.9 (7)		35	20.6 (7)	
% use of melatonin supplements (n)	37	0 (0)		35	5.7 (2)	
LEDD	37	700 [434]	[0, 2125]	35	590 [407]	[0, 1940]
UPDRS-III	37	23.9 [10.5]	[8, 55]	35	20.7 [8.8]	[8, 50]
H&Y stage	37			35		
% Stage 1.0 (n)		3 (1)			11 (4)	
% Stage 1.5 (n)		3 (1)			0 (0)	
% Stage 2.0 (n)		51 (19)			66 (23)	
% Stage 2.5 (n)		19 (7)			11 (4)	
% Stage 3.0 (n)		19 (7)			6 (2)	
% Stage 4.0 (n)		3 (1)			6 (2)	
% Stage 5.0 (n)		3 (1)			0 (0)	
MMSE	37	28.0 [1.7]	[24, 30]	35	28.4 [2.3]	[21, 30]
HDRS	37	14.5 [3.8]	[8, 25]	35	14.7 [3.5]	[9, 24]
GDS-30	37	17.1 [5.9]	[3, 28]	35	17.9 [5.9]	[6, 28]
DSM-IV-TR classification comorbid conditions	37			35		
% Cognitive disorder (n)*		5 (2)			9 (3)	
% Anxiety disorder (n)†		43 (16)			60 (21)	
% Substance-related disorder (n)†		3 (1)			0 (0)	
SCOPA SLEEP	37			35		
Night-time sleep		7.9 [4.3]	[0, 15]		9.3 [3.8]	[1, 15]
Daytime sleepiness		6.7 [5.0]	[0, 18]		6.2 [4.3]	[0, 15]
Sleep quality rating		3.5 [1.8]	[0, 6]		4.3 [1.5]	[0, 6]
Total		14.5 [7.1]	[2, 33]		15.5 [6.3]	[2, 28]
CSD subjective sleep rating	36	2.0 [0.8]	[0,3]	35	1.7 [0.6]	[1, 3]
TST (min)	29	391 (57)	[254, 524]	35	386 (67)	[246, 533]
SF (wake bouts/ hr)	29	7.0 (4.1)	[1.7, 18.1]	35	6.2 (2.8)	[2.5, 15.6]
SE (%)	29	86 [6]	[71, 94]	35	87 [9]	[63, 97]
MEQ total	37	54.0 [8.5]	[38, 74]	34	56.0 [9.1]	[35, 72]

Table 1, continued

Variable	Control group			Intervention group		
	n	Mean [SD]	Range	n	Mean [SD]	Range
Chronotype	37			34		
% Moderate evening type (n)		8 (3)			3 (1)	
% Neutral type (n)		57 (21)			65 (22)	
% Moderate morning type (n)		30 (11)			24 (8)	
% Distinct morning type (n)		5 (2)			9 (3)	
Cortisol [pg/l]						
AUCg	24	25.0 [10.2]	[9.2, 39.4]	22	21.8 [10.2]	[10.7, 52.3]
AUCi	24	3.3 [9.3]	[-14.0, 21.9]	22	5.7 [9.2]	[-6.8, 24.5]
Mean evening concentration	20	2.3 [0.5]	[1.9, 3.9]	20	2.7 [1.6]	[1.9, 5.6]
WHO-QOL	37	80.7 [11.9]	[58, 112]	35	79.0 [13.1]	[46, 106]
ZBI	31	25.3 [12.6]	[3, 56]	29	23.3 [16.4]	[3, 62]

LEDD = levodopa equivalent daily dose; HDRS = Hamilton Depression Rating Scale; GDS-30 = 30-item Geriatric Depression Rating Scale; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease - Sleep; CSD = Consensus Sleep Diary; TST = total sleep time; SF = sleep fragmentation; SE = sleep efficiency; UPDRS-III = section III of the Unified Parkinson's Disease Rating Scale; MMSE = Mini Mental State Examination; MEQ = Morningness – Eveningness Questionnaire; AUCG = area under the curve with respect to the ground, AUCI = area under the curve with respect to the index of salivary cortisol change over time; WHO-QOL = World Health Organization Quality of Life assessment; ZBI = Zarit Burden Interview

* Obtained from the medical history, provided by the general practitioner or neurologist, † Established with the Structured Clinical Interview for DSM-IV Axis I Disorders

Efficacy analyses

Table 2 demonstrates the results of our crude efficacy analyses, corrected only for baseline value of the outcome variable. The adjusted analyses, corrected for confounders, are presented in Table 3.

During the intervention, the HDRS total score decreased in both the intervention and control group. At T2, there was no significant between-group difference in our primary outcome ($p = 0.59$). At T5, the HDRS score was significantly lower in the control group than the intervention group ($p = 0.03$).

When looking at secondary outcomes, the mean GDS-30 score decreased in both groups, with no significant between-group differences. The percentage of participants that achieved clinical remission of the depressive episode at T2 was 63% in the intervention group and 52% in the control group, corresponding to an Absolute Risk Reduction (ARR) of 0.11 and Number Needed to Treat (NNT) of 9. At T5, 72% of participants in the experimental

group had recovered from their depressive episode, versus 87% of the control group (ARR = 0.15, NNT = 7). At both time points, this difference was statistically not significant (n.s.).
The score on the total SCOPA-SLEEP and its subscales decreased in both groups during the intervention, with no significant between-group differences. Between T0 and T2, TST decreased in both groups. Sleep fragmentation increased in the control group, while it remained relatively stable in the intervention group (between-group difference at T2 and T5 (n.s.).
The mean AUC_G of the morning salivary cortisol concentrations in the intervention group decreased between T0 and T2, while it increased in the control group, resulting in a significant difference at T2 ($p = 0.04$). At T5, this difference was not significant. There were no significant between-group differences for the AUC_I.

The exploratory analyses showed no significant between-group differences, except for the subjective quality of sleep at T2, which was rated better on the CSD in the intervention group ($p = 0.04$).

Adverse effects and treatment satisfaction

In the intervention group, 66% experienced adverse effects, compared to 46% of the control group ($\chi^2 = 2.68$, $df = 1$, $p = 0.10$). Ocular symptoms, headache, and gastro-intestinal complaints were reported most often. All adverse effects were mild and transient. There were no significant between-group differences in the occurrence of adverse events, or in the appreciation of duration and timing of light therapy sessions.

Table 2: **Results of the crude treatment efficacy analyses corrected for baseline value.**

	Baseline (T0)		Post-intervention (T2)					Post-follow-up (T5)				
	Control (n = 37)	BLT (n = 35)	Control (n = 34)	BLT (n = 33)	Group difference			Control (n = 29)	BLT (n = 30)	Group difference		
	Mean [SD]	Mean [SD]	Mean [SD]	Mean [SD]	B [SE]	95% CI	P	Mean [SD]	Mean [SD]	B [SE]	95% CI	p
HDRS	14.5 [3.8]	14.7 [3.5]	8.3 [4.3]	7.6 [5.0]	-0.58 [1.06]	-2.66, 1.51	0.59	5.9 [3.0]	8.5 [4.6]	2.39 [1.10]	0.23, 4.57	0.03
GDS-30	17.1 [5.9]	17.9 [5.9]	14.9 [6.3]	13.7 [6.9]	-1.36 [1.39]	-4.08, 1.37	0.33	12.3 [7.0]	13.2 [6.6]	0.36 [1.40]	-2.40, 3.11	0.80
% remission (n) *	0 (0)	0 (0)	52 (17)	63 (20)	0.57 [0.51]	0.43, 1.57	0.26	87 (26)	72 (21)	-0.91 [0.68]	-2.24, 0.42	0.18
SCOPA-SLEEP												
Night-time sleep	7.9 [4.3]	9.3 [3.8]	5.1 [3.3]	5.5 [3.5]	-0.52 [0.72]	-1.94, 0.90	0.47	4.4 [3.7]	6.1 [3.2]	0.83 [0.87]	-0.88, 2.55	0.34
Daytime sleepiness	6.7 [5.0]	6.2 [4.3]	5.6 [3.8]	5.5 [3.6]	0.07 [0.76]	-1.44, 1.57	0.93	5.3 [4.0]	5.1 [3.8]	0.24 [0.77]	-1.28, 1.76	0.76
Sleep quality rating	3.5 [1.8]	4.3 [1.5]	2.2 [1.5]	2.3 [1.5]	-0.24 [0.33]	-0.90, 0.42	0.48	2.4 [1.7]	2.8 [1.5]	0.04 [0.34]	-0.62, 0.71	0.91
Total	14.5 [7.1]	15.5 [6.3]	10.8 [5.5]	10.9 [6.0]	-0.62 [1.23]	-2.93, 1.90	0.67	9.7 [6.1]	11.2 [5.4]	0.99 [1.24]	-1.44, 3.43	0.42
CSD subjective sleep	2.0 [0.8]	1.7 [0.6]	2.1 [0.7]	2.2 [0.8]	0.32 [0.16]	0.01, 0.62	0.04	2.2 [0.77]	2.0 [0.62]	0.00 [0.16]	-0.32, 0.32	0.98
TST (minutes)	391 [57]	386 [67]	349 [39]	371 [56]	26.71 [13.51]	0.08, 53.35	0.05	363 [69]	375 [67]	-6.11 [14.51]	-34.72, 22.50	0.68
SF (wake bouts/hr)	7.0 [4.1]	6.2 [2.8]	8.2 [5.6]	6.3 [2.9]	-0.51 [0.68]	-1.86, 0.84	0.46	8.0 [3.3]	6.1 [2.8]	-0.48 [0.73]	-1.92, 0.97	0.52
SE (%)	86 [6]	87 [9]	84 [8]	86 [7]	1.73 [1.32]	-0.88, 4.34	0.19	81 [8]	85 [9]	2.11 [1.43]	-0.71, 4.93	0.14
UPDRS-III	23.9 [10.5]	20.7 [8.8]	24.1 [10.1]	18.2 [7.4]	-2.76 [1.81]	-6.35, 0.83	0.13	23.0 [12.0]	21.3 [11.0]	1.34 [1.92]	-2.46, 5.13	0.49
MMSE	28.0 [1.7]	28.4 [2.3]	28.0 [2.8]	28.3 [2.7]	-0.02 [0.49]	-0.98, 0.95	0.97	28.1 [2.6]	28.2 [2.7]	0.06 [0.50]	-0.94, 1.05	0.91
MEQ total	54.0 [8.5]	56.0 [9.1]	53.9 [6.7]	57.4 [7.9]	1.37 [1.33]	-1.24, 3.99	0.30	55.3 [6.6]	57.3 [6.8]	0.76 [1.34]	-1.89, 3.40	0.57
Cortisol (pg/l)												
AUC_G	25.0 [10.2]	23.1 [10.2]	26.9 [19.6]	19.6 [7.8]	-8.11 [3.93]	-15.77, -0.35	0.04	28.4 [17.5]	27.2 [10.8]	-0.96 [3.96]	-8.77, 6.85	0.81
AUCI	3.3 [9.3]	5.6 [9.2]	8.0 [15.2]	3.0 [7.9]	-4.95 [3.98]	-12.81, 2.92	0.22	3.8 [12.8]	5.7 [14.4]	1.59 [4.03]	-6.36, 9.54	0.69
Mean evening Concentration	2.3 [0.5]	2.7 [1.6]	7.2 [19.1]	3.9 [5.2]	-3.43 [2.72]	-8.82, 1.95	0.21	2.7 [0.9]	2.1 [0.5]	-0.52 [2.93]	-6.31, 5.27	0.86

Table 2, continued

WHO-QOL	80.7 [11.9]	79.0 [13.1]	83.2 [11.8]	83.3 [13.6]	0.48 [2.55]	-4.57, 5.54	0.85	83.1[13.5]	85.5 [12.6]	2.65 [2.59]	-2.48, 7.77	0.31
ZBI	25.3 [12.6]	23.3 [16.4]	20.7 [10.1]	21.1 [15.8]	1.44 [2.52]	-3.57, 6.45	0.44	21.7 [16.2]	19.9 [13.5]	-1.28 [2.56]	-6.37, 3.81	0.62

* analysed using logistic regression analysis;

HDRS = Hamilton Depression Rating Scale; GDS-30 = 30-item Geriatric Depression Rating Scale; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease - Sleep; CSD = Consensus Sleep Diary; TST = total sleep time; SF = sleep fragmentation; SE = sleep efficiency; UPDRS-III = section III of the Unified Parkinson's Disease Rating Scale; MMSE = Mini Mental State Examination; MEQ = Morningness – Eveningness Questionnaire; AUCG = area under the curve with respect to the ground, AUCI = area under the curve with respect to the index of salivary cortisol change over time; WHO-QOL = abbreviated version of the World Health Organization Quality of Life assessment; ZBI = Zarit Burden Interview

Table 3: **Results of the treatment efficacy analyses corrected for baseline value and confounders.**

	Baseline (T0)		Post-intervention (T2)					Post-follow-up (T5)				
	Control (n = 37)	BLT (n = 35)	Control (n = 34)	BLT (n = 33)	Group difference			Control (n = 29)	BLT (n = 30)	Group difference		
	Mean [SD]	**Mean [SD]**	**Mean [SD]**	**Mean [SD]**	**B [SE]**	**95% CI**	**p**	**Mean [SD]**	**Mean [SD]**	**B [SE]**	**95% CI**	**p**
HDRS	14.5 [3.8]	14.7 [3.5]	8.3 [4.3]	7.6 [5.0]	0.01 [1.15]	-2.25, 2.27	0.99	5.9 [3.0]	8.5 [4.6]	2.93 [1.22]	0.53, 5.34	0.02
GDS-30	17.1 [5.9]	17.9 [5.9]	14.9 [6.3]	13.7 [6.9]	-0.42 [1.60]	-3.57, 2.74	0.80	12.3 [7.0]	13.2 [6.6]	0.21 [1.65]	-3.04, 3.46	0.90
% remission (n) *	0 (0)	0 (0)	52 (17)	63 (20)	-0.23 [0.83]	-1.86, 1.40	0.78	87 (26)	72 (21)	-1.53 [1.18]	-3.84, 0.78	0.20
SCOPA-SLEEP												
Night-time sleep	7.9 [4.3]	9.3 [3.8]	5.1 [3.3]	5.5 [3.5]	0.31 [0.88]	-1.42, 2.05	0.72	4.4 [3.7]	6.1 [3.2]	0.94 [0.99]	-1.02, 2.90	0.34
Daytime sleepiness	6.7 [5.0]	6.2 [4.3]	5.6 [3.8]	5.5 [3.6]	0.94 [0.83]	-0.69, 2.58	0.26	5.3 [4.0]	5.1 [3.8]	1.44 [0.86]	-0.26, 3.14	0.10
Sleep quality rating	3.5 [1.8]	4.3 [1.5]	2.2 [1.5]	2.3 [1.5]	0.05 [0.38]	-0.70, 0.80	0.89	2.4 [1.7]	2.8 [1.5]	0.06 [0.40]	-0.72, 0.85	0.87
Total	14.5 [7.1]	15.5 [6.3]	10.8 [5.5]	10.9 [6.0]	1.22 [1.36]	-1.46, 3.89	0.37	9.7 [6.1]	11.2 [5.4]	2.41 [1.41]	-0.37, 5.18	0.09
CSD subjective sleep	2.0 [0.8]	1.7 [0.6]	2.1 [0.7]	2.2 [0.8]	0.36 [0.18]	0.01, 0.70	<0.05	2.2 [0.77]	2.0 [0.62]	0.14 [0.19]	-0.23, 0.51	0.46
TST (minutes)	391 [57]	386 [67]	349 [39]	371 [56]	27.51 [15.53]	-3.17, 58.18	0.08	363 [69]	375 [67]	2.59 [17.00]	-30.98, 36.16	0.88
SF (wake bouts/hr)	7.0 [4.1]	6.2 [2.8]	8.2 [5.6]	6.3 [2.9]	-0.42 [0.82]	-2.04, 1.20	0.61	8.0 [3.3]	6.1 [2.8]	-0.69 [0.89]	-2.44, 1.06	0.44
SE (%)	86 [6]	87 [9]	85 [8]	86 [7]	1.06 [1.55]	-1.99, 4.12	0.49	81 [8]	85 [9]	3.16 [1.70]	-0.20, 6.51	0.07
UPDRS-III	23.9 [10.5]	20.7 [8.8]	24.1 [10.1]	18.2 [7.4]	-2.31 [2.29]	-6.85, 2.24	0.32	23.0 [12.0]	21.3 [11.0]	3.75 [2.51]	-1.24, 8.73	0.14
MMSE	28.0 [1.7]	28.4 [2.3]	28.0 [2.8]	28.3 [2.7]	0.00 [0.43]	-0.85, 0.86	0.99	28.1 [2.6]	28.2 [2.7]	-0.21 [0.47]	-1.14, 0.73	0.66
MEQ total	54.0 [8.5]	56.0 [9.1]	53.9 [6.7]	57.4 [7.9]	1.40 [1.72]	-1.98, 4.79	0.42	55.3 [6.6]	57.3 [6.8]	0.93 [1.75]	-2.53, 4.38	0.60
Cortisol (pg/l)												
AUC_G	25.0 [10.2]	23.1 [10.2]	26.9 [19.6]	19.6 [7.8]	-13.45 [5.17]	-23.69, -3.22	0.01	28.4 [17.5]	27.2 [10.8]	-6.36 [5.33]	-16.91, 4.20	0.24
AUCI	3.3 [9.3]	5.6 [9.2]	8.0 [15.2]	3.0 [7.9]	-0.94 [5.73]	-12.28, 10.39	0.87	3.8 [12.8]	5.7 [14.4]	1.32 [5.91]	-10.38, 13.02	0.82
Mean evening Concentration	2.3 [0.5]	2.7 [1.6]	7.2 [19.1]	3.9 [5.2]	2.12 [1.65]	-1.16, 5.39	0.20	2.7 [0.9]	2.1 [0.5]	2.07 [1.91]	-1.73, 5.87	0.28

Table 3, continued

WHO-QOL	80.7 [11.9]	79.0 [13.1]	83.2 [11.8]	83.3 [13.6]	-0.34 [2.90]	-6.27, 5.59	0.91	83.1 [13.5]	85.5 [12.6]	1.16 [3.11]	-5.02, 7.35	0.71
ZBI	25.3 [12.6]	23.3 [16.4]	20.7 [10.1]	21.1 [15.8]	1.91 [3.22]	-4.51, 8.34	0.55	21.7 [16.2]	19.9 [13.5]	-1.28 [3.61]	-8.50, 5.93	0.72

* analysed using logistic regression analysis;

HDRS = Hamilton Depression Rating Scale; GDS-30 = 30-item Geriatric Depression Rating Scale; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease - Sleep; CSD = Consensus Sleep Diary; TST = total sleep time; SF = sleep fragmentation; SE = sleep efficiency; UPDRS-III = section III of the Unified Parkinson's Disease Rating Scale; MMSE = Mini Mental State Examination; MEQ = Morningness – Eveningness Questionnaire; AUC_I = Area under the curve with respect to the index of salivary cortisol change over time; AUC_G = area under the curve with respect to the ground; WHO-QOL = abbreviated version of the World Health Organization Quality of Life assessment; ZBI = Zarit Burden Interview

Table 4: **Results of the *post hoc* analyses: a mixed models analysis on the effect of time for the mITT population.**

	Baseline (T0) (n = 72)	Post-intervention (T2) (n = 67)				Post-follow-up (T5) (n = 59)			
	Mean [SD]	**Mean [SD]**	**B [SE]**	**95% CI**	**p**	**Mean [SD]**	**B [SE]**	**95% CI**	**p**
HDRS	14.6 [3.6]	8.0 [4.6]	-6.5 [0.6]	[5.3, 7.6]	<0.001	7.2 [4.0]	-7.1 [0.6]	[5.8, 8.3]	<0.001
GDS-30	17.4 [5.9]	14.3 [6.6]	-2.9 [0.6]	[1.6, 4.1]	<0.001	12.7 [6.8]	-4.2 [0.6]	[3.0, 5.5]	<0.001
SCOPA-SLEEP									
Night-time sleep	8.6 [4.1]	5.3 [3.4]	-3.2 [0.4]	[2.4, 4.0]	<0.001	5.3 [3.5]	-3.1 [0.4]	[2.3, 3.9]	<0.001
Daytime sleepiness	6.4 [4.7]	5.6 [3.7]	-0.8 [0.4]	[0.1, 1.6]	0.04	5.2 [3.9]	-1.2 [0.4]	[0.4, 2.0]	<0.01
Sleep quality rating	3.9 [1.7]	2.2 [1.5]	-1.7 [0.2]	[1.3, 2.0]	<0.001	2.6 [1.6]	-1.3 [0.2]	[1.0, 1.7]	<0.001
Total	15.0 [6.7]	10.9 [5.7]	-4.0 [0.6]	[2.8, 5.3]	<0.001	10.5 [5.8]	-4.3 [0.6]	[3.1, 5.6]	<0.001
CSD subjective sleep	1.8 [0.7]	2.2 [0.7]	0.3 [0.1]	[-0.5, -0.2]	<0.001	2.1 [0.7]	0.2 [0.1]	[-0.4, -0.1]	<0.01
TST (minutes)	388 [63]	360 [50]	-14.5 [6.9]	[0.8, 28.2]	0.04	370 [68]	-2.7 [7.2]	[-11.5, 16.9]	0.71
SF (wake bouts/hr)	6.6 [3.5]	7.2 [4.5]	0.1 [0.4]	[-0.6, 0.9]	0.69	6.9 [3.2]	0.2 [0.4]	[-0.5, 0.9]	0.62
SE(%)	86.9 [7.7]	85.6 [7.4]	0.3 [0.7]	[-1.1, 1.7]	0.67	83.2 [8.4]	3.2 [0.8]	[1.7, 4.7]	<0.001
UPDRS-III	22.4 [9.8]	21.2 [9.3]	-1.2 [1.0]	[-0.8, 3.1]	0.23	22.2 [11.5]	0.5 [1.0]	[-1.5, 2.5]	0.62
MMSE	28.2 [2.0]	28.1 [2.7]	-0.05 [0.2]	[-0.4, 0.5]	0.85	28.2 [2.6]	-0.03 [0.2]	[-0.4, 0.5]	0.89
MEQ total	54.9 [8.8]	55.7 [7.5]	0.1 [0.6]	[-1.3, 1.1]	0.83	56.3 [6.7]	0.7 [0.6]	[-1.9, 0.5]	0.27
Cortisol (pg/l)									
AUCg	24.1 [10.1]	23.7 [15.9]	0.5 [2.0]	[-3.5, 4.5]	0.82	27.9 [14.9]	3.4 [2.0]	[-7.4, 0.7]	0.10
AUCi	4.6 [9.4]	5.8 [12.7]	0.9 [2.4]	[-5.6, 3.8]	0.70	4.6 [13.4]	0.5 [2.4]	[-4.3, 5.2]	0.84
Mean evening concentration	2.4 [0.9]	5.6 [14.0]	3.3 [1.5]	[-6.2, -0.3]	0.03	2.4 [0.7]	0.1 [1.6]	[-3.3, 3.0]	0.94
WHO-QOL	79.9 [12.4]	83.2 [12.7]	2.6 [1.3]	[-5.1, -0.1]	0.04	84.3 [13.0]	3.1 [1.3]	[-5.7, -0.6]	0.02
ZBI	24.3 [14.4]	20.9 [15.9]	-2.9 [1.3]	[0.3, 5.4]	0.03	20.7 [14.7]	3.3 [1.3]	[0.7, 5.8]	0.013

HDRS = Hamilton Depression Rating Scale; GDS-30 = 30-item Geriatric Depression Rating Scale; SCOPA-SLEEP = Scales for Outcomes in Parkinson's Disease - Sleep; CSD = Consensus Sleep Diary; TST = total sleep time; SF = sleep fragmentation; SE = sleep efficiency; UPDRS-III = section III of the Unified Parkinson's Disease Rating Scale; MMSE = Mini Mental State Examination; MEQ = Morningness – Eveningness Questionnaire; AUC_I = Area under the curve with respect to the index of salivary cortisol change over time; AUC_G = area under the curve with respect to the ground; WHO-QOL = abbreviated version of the World Health Organization Quality of Life assessment; ZBI = Zarit Burden Interview

Discussion

In this RCT, we studied the effects of BLT on depression severity as the primary outcome in patients with PD and MDD. This interventional study provides Class II evidence that BLT (10,000 Lux) is not superior to a control light device (200 Lux) in reducing depressive symptoms, as measured with the HDRS, in PD patients with MDD (B (SE) = -0.58 (1.06), 95% CI -2.66 to 1.51, $p = 0.59$). Comparison of this RCT to previous studies on the effects of BLT on depressive symptoms in PD patients is difficult, as prior studies differed in study design, study population, control condition and measuring instruments, but also in type, duration and timing of light exposure. Previous studies, however, did show a positive effect of BLT on mood (10-12). In a case series of 12 patients with PD and insomnia and/or depressive symptoms, two to five weeks of 1000-1500 Lux BLT for 60 to 90 minutes prior to normal bedtime resulted in a noticeable improvement of mood, as well as sleep onset latency and sleep continuity (12). An open label study on the effects of 4000 to 6000 Lux BLT for 60 minutes prior to bedtime in 120 PD patients resulted in less anxiety and improved mood in patients with good compliance (11). In a randomized controlled study in 36 PD patients, two weeks of 7500 Lux BLT for 30 minutes each morning resulted in a stronger improvement of mood and daytime sleepiness, as compared to 950 Lux placebo light (10). In a recent RCT, 31 PD patients were treated for two weeks with 10,000 Lux BLT or 300 Lux dim-red light, twice daily for 60 minutes (13). BLT resulted in significant improvements of EDS and subjective sleep quality.

Since we observed a large improvement of mood and sleep in our trial in both the group treated with BLT and the group treated with a control light device, we assessed the effect of time on our outcomes in a *post hoc* linear mixed models analysis (see Table 4). There was a significant effect of time on depression, as measured with the HDRS (post-intervention: $p < 0.001$, post-follow-up: $p < 0.001$). There are several possible explanations for this finding. The first is a spontaneous remission. In approximately 50% of the depressed PD patients in a 5-year longitudinal cohort study, depression showed a non-persistent course (35). Although our treatment phase only lasted three months, some participants may have shown a spontaneous remission of their depression. A second possibility is a placebo-effect. Average placebo response rates in placebo-controlled antidepressant trials, defined as a ≥ 50% reduction in HDRS score from baseline, are 35% to 40% (36). A *post hoc* analysis showed that the response rate in our control group was 44%, as compared to 56% in the intervention group, which is a bit higher than in antidepressant trials. A final possible explanation, is that the decrease in depressive symptoms was due to structuring of the sleep-wake cycle as a result of the scheduling of LT. All study participants had to get up at a fixed time for their morning LT, and were advised to go to bed approximately one hour after evening LT. According to the '*social zeitgeber*' hypothesis, mood can be improved by restoring the circadian rhythm by re-establishing daily routine, such as bed and wake-up time (37). To explore this hypothesis, we performed a *post hoc* analysis, correlating the change in HDRS score to the change in average standard deviation of bedtime and time of getting up between T0 and T2. This correlation was not significant. Our study was, however, not designed to test the effects of improvement of the sleep-wake rhythm on depressive symptoms. To disentangle the effects of structuring the sleep-wake cycle from the effects of BLT, a future study design should have three additional treatment arms: two where BLT and control light are administered at random times, and one where the participants apply a scheduled sleep-wake cycle without receiving LT.

Subjective sleep improved significantly in both groups during the intervention (see Table 4). The CSD subjective sleep rating increased significantly more in the intervention group, as compared to the control group. This finding supports the hypothesis that BLT has a positive effect on subjective sleep in PD, as also shown in previous studies (11-13).
When looking at circadian rhythm markers, the AUC_G decreased in the BLT group during treatment, while it increased in the control group, resulting in a significant between-group difference at T2. In previous studies in non-PD samples, BLT led to a decrease in total cortisol secretion throughout the day (38). Since increased cortisol levels are associated with light sleep (39), we hypothesize that the improvement of subjective sleep in the BLT group is related to decreased cortisol levels. Unfortunately, our own data could not support this hypothesis: a *post hoc* correlation between the change in AUCg and the change in CSD subjective sleep rating between T0 and T2 was not significant, possibly because the number of calculated AUCg changes was too small.

This RCT had several limitations. Our power analysis indicated a necessary sample size of 84 participants. Since we were able to enrol only 83 participants and our drop-out rate was higher than expected, we had insufficient power for our follow-up analyses. Moreover, we were unable to collect all data from all study participants on objective sleep parameters and salivary melatonin and cortisol concentrations. Especially the collection of saliva samples at set times was experienced as stressful by the participants, and these samples were not collected at all six days by all participants. We therefore think that we were underpowered for some of the analyses on the secondary outcomes. However, the sample size was sufficiently large for the post-intervention analysis of our primary outcome.
Our study participants had a mean HDRS score of 14.6 [3.6] at baseline, which makes generalizability of our results to PD patients with more severe depression questionable. However, all participants did meet criteria for MDD according to the DSM-IV-TR.
We cannot rule out that the decrease of depressive symptoms in the control group was partially due to a therapeutic effect of the control light, since a study in healthy participants suggests that a light intensity of approximately 100 lux is already sufficient to influence the circadian rhythm (40). However, the participants in that study were exposed to 100

Lux for 6.5 hours (40), while our controls were only exposed to 30 minutes of 200 lux twice daily.

At the end of the trial, the HDRS score was significantly lower in the control group. We chose a naturalistic follow-up design, because we found it unethical to withhold treatment from patients with remaining depressive symptom for six months. Since the number of participants with persistent MDD in the control group was larger post-intervention, more participants in this group may have been inclined to seek treatment during follow-up. This is reflected by the medication use of our participants during follow-up. At the end of the intervention, 7/34 (20.6%) of participants in the experimental group used antidepressants, and 8/30 (26.7%) in the control group. During follow-up, the number of users of antidepressants decreased more strongly in the experimental group, to 4/29 (13.8%), versus 6/32 (18.8%) in the control group at the end of the trial. While we corrected our efficacy analyses for the use of antidepressants or anxiolytic/hypnotic medications, we were unable to correct for the effect of psychotherapeutic or behavioral interventions. This might explain the larger improvement of depressive symptoms at follow-up in the control group.

Finally, we encountered some issues in the collection and analysis of the saliva samples during our trial, which precluded us from calculating reliable values for the DLMO, evening AUC_G and AUC_I.

In conclusion, BLT was not more effective in reducing depressive symptoms than exposure to control light. Both the intervention and control group showed a significant improvement of depression and subjective sleep. However, BLT was more effective in improving subjective sleep quality than control light, possibly through a BLT-induced decrease in cortisol levels.

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Chapter 10

General Discussion

Introduction

Part 1 of this thesis (**Chapters 2 to 4**) aimed at gaining a better understanding of anxiety, depression and sleep disorders in Parkinson's disease (PD), their interaction with one another and with other PD-related symptoms, providing potential starting points for the improvement of the diagnostic process in clinical practice. *Part 2* (**Chapters 5 to 8**) focused on treatment. In this part, the effects of psychological interventions on psychological distress in PD are discussed, and Light Therapy (LT) is introduced as an adjuvant treatment option in PD, and a non-pharmacological alternative for the treatment of major depressive disorder (MDD) in PD patients.

In this final chapter, I will review the results of our studies in the context of the existing literature and describe their methodological limitations. Moreover, I will discuss the implications for routine clinical practice and provide potential directions for future research.

Summary

Part 1 of this thesis comprises epidemiological studies on anxiety, depression and insomnia in PD. In **Chapter 2**, we present a cross-sectional study on anxiety in 294 PD patients (1). We studied the phenomenon of anxiety in PD by performing a principal component analysis to identify the different underlying symptom dimensions of anxiety, as measured with the Beck Anxiety Inventory (BAI). This analysis showed that the items of the BAI can be subdivided into five symptom dimensions, or subscales: one affective subscale and four subscales measuring somatic symptoms of anxiety. We assessed the overlap between the identified subscales of the BAI and scores on instruments assessing other PD-related symptoms, including motor dysfunction, autonomic failure and depressive symptoms. These analyses demonstrated a significant association between the somatic symptom subscales of the BAI and the scores on instruments measuring motor and autonomic dysfunction. The affective subscale did not show this association and may thus be relatively uninfluenced by somatic symptoms. The total BAI score as well as the scores on its subscales showed an association with the inventory measuring symptoms of depression, demonstrating a strong relationship between anxiety and depression in PD.

Since the diagnosis of anxiety in PD is complicated, recognition in daily practice may benefit from increased knowledge of risk factors for anxiety in PD patients. In **Chapter 3**, we present the results of a longitudinal study on the predictors of anxiety in PD (2). For this study, we used data from the Parkinson's Progression Markers Initiative (PPMI), selecting 306 *de novo* PD patients that were not using psychiatric medications at baseline.

We identified four predictors of anxiety: depression, PD-related impulsive or compulsive behaviors (ICBs), cognitive dysfunction and REM-sleep behavior disorder (RBD). We found that the course of symptoms of both depression and ICBs was similar to the course of anxiety over two years of follow-up, with more severe symptoms at baseline and an average decrease of these neuropsychiatric symptoms over time. The presence of RBD or more severe cognitive dysfunction at baseline were predictors of an increase in anxiety during follow-up.

Chapters 2 and 3 demonstrated a relationship between sleep, anxiety and depression in PD. In **Chapter 4** of this thesis, we studied the temporal relationship of these symptoms: we investigated whether insomnia is a risk factor for the development of depression and anxiety, or, vice versa, whether anxiety and depression are predictors of insomnia in PD patients (3). For this study, we selected PD-medication free patients of the PPMI cohort (n = 361). The presence of insomnia at baseline was associated with higher levels of anxiety and depression after six months of follow-up. Vice versa, subjects with more severe symptoms of anxiety or depression at baseline also had a higher risk of developing insomnia over time. This indicates that the relationship between anxiety / depression and insomnia is bidirectional in PD patients.

In *Part 2* of this thesis, we shift focus from diagnostics to treatment. In **Chapter 5**, we present the results of a meta-analysis on the efficacy of Cognitive Behavioral Therapy (CBT) and Mindfulness-based therapies (MBTs) on psychological distress in patients with PD and two other neurodegenerative disorders, namely Huntington's disease (HD) and Multiple Sclerosis (MS) (4). We found no RCTs on psychological interventions in HD populations. The studies in patients with PD and MS had small to moderate effect sizes. Although these studies were characterized by a high degree of heterogeneity and the overall methodological quality was insufficient, the results of our meta-analysis suggest that psychological interventions can have a positive – but modest – effect on psychological distress in MS and PD patients.

In **Chapter 6**, we introduce LT as a non-pharmacological treatment option for insomnia and depression in PD (5). We hypothesize that the observed association between depression and sleep disorders in PD patients is due to a common underlying pathophysiological mechanism, namely a disturbance of the circadian system. In this narrative review, we describe how the circadian system of PD patients can be negatively influenced by multiple factors, causing conflicting input of *zeitgebers* to the circadian pacemaker. This may lead to a desynchronization of the circadian rhythm relative to the 24-hour societal rhythm. Indeed, there is scientific evidence for a phase-advanced circadian rhythm in PD patients. LT can resynchronize the circadian rhythm with the societal rhythm, providing an alternative treatment option for PD patients suffering from depression and sleep disorders. Previously published studies on the efficacy of LT in PD patients demonstrate positive effects on sleep, mood and motor function. However, no randomized-controlled trial (RCT) on the effects of LT in PD had been performed yet. Therefore, we performed two RCTs on the efficacy of LT on motor and non-motor symptoms of PD, as presented in the following chapters.

Chapter 7 describes the findings of a multicenter double-blind RCT on the safety and effectiveness of Spectramax LT as an adjunctive treatment for motor and non-motor symptoms in PD patients. We randomized 92 participants to receive daily one-hour treatment of Spectramax LT, or control LT with a bandwidth that was thought to be biologically inactive. We did not find significant differences between the group receiving Spectramax LT and the control group on the primary outcome, the change from baseline to end of treatment on the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I + II + III composite score, which is a measure for severity of both motor and non-motor symptoms. However, we did find significantly larger improvements in severity of non-motor symptoms, including neuropsychiatric symptoms, and health-related quality of life in the group receiving Spectramax LT. Moreover, we saw a trend effect on excessive daytime sleepiness (EDS). Spectramax LT was generally well tolerated: although neurological adverse effects were reported more often in the Spectramax LT group than in the control group, all adverse effects were clinically non-significant and no serious adverse events occurring during the trial were attributed to treatment.

Chapter 8 describes the study protocol for a double-blind RCT on the efficacy of LT in the treatment of depression in PD (6). Eligible patients for this trial were patients with PD and MDD. Participants in the intervention group were treated twice daily with 30 minutes of Bright LT (BLT), while the control group was treated with a control device, emitting light with an intensity that was thought to be of no influence on the circadian system. The primary outcome of the study was depression, operationalized as the change in Hamilton Depression Rating Scale (HDRS) score between baseline and end of treatment. Secondary outcomes were alternative depression measures, objective and subjective sleep measures, and salivary melatonin and cortisol concentrations. For exploratory purposes, we also assessed the effects on motor symptoms, quality of life and caregiver burden. In this chapter, we also discussed the methodological challenges of performing a placebo-controlled trial of LT (see 'Methodological considerations' below).

In **Chapter 9**, we presented the results of this RCT. We included 83 patients with a diagnosis of both idiopathic PD and MDD. During treatment, the HDRS score decreased in both groups, without a significant between-group difference. Moreover, subjective sleep improved in both groups, with a significantly larger improvement of subjective sleep quality in the experimental group. In the group receiving BLT, total salivary cortisol secretion decreased, while it increased in the control group, resulting in a significant between-group difference at the end of treatment.

Synthesis

In clinical practice, PD patients often present with a complex mixture of motor and non-motor symptoms, complicating both the diagnostic process and treatment. In this synthesis of our study findings, I give a description of the overlap, co-occurrence and temporal relationship between PD-related anxiety, depression and sleep disorders, and other (non-)motor symptoms. Moreover, I present various hypotheses for the underlying etiology, with a specific interest in the circadian system.

The overlap and interaction between motor and non-motor symptoms in PD

In **Chapter 2**, we demonstrated that there is an overlap between PD-related anxiety and symptoms of motor and autonomic failure. The diagnosis of anxiety in PD patients is complicated, as both PD and anxiety disorders are accompanied by somatic symptoms, posing challenges for clinical practice. E.g., somatic symptoms like trembling and light-headedness in an anxious PD patient may be somatic anxiety equivalents, but could also be attributable to motor and autonomic dysfunction. However, somatic symptoms do form an integral part of anxiety (7), and anxiety, motor symptoms and autonomic failure are intertwined in PD (8-10). The distinction between anxiety and symptoms of motor and autonomic failure may therefore be artificial. A more integrated psychosomatic concept of anxiety, that captures the perception of these symptoms from a patient's perspective, might correspond to the subjective experience of anxiety better. This will be discussed further in the section on directions for future research.

The cross-sectional study presented in **Chapter 2** showed not only an association between anxiety and somatic symptoms, but also between anxiety and depression. The longitudinal study in **Chapter 3** also found a relationship between symptoms of anxiety and depression, showing a parallel course over a follow-up period of two years. Our findings are in line with previous studies, demonstrating a co-occurrence of anxiety and depressive disorders in 19 to 40% of patients with PD, which is higher than in matched controls (11-13). Due to the high comorbidity of anxiety and depression in PD, and the evidence for a shared underlying neuropathological process, various authors have suggested that developing a new diagnostic category of mixed anxiety-depression might be relevant for PD patients (12, 14, 15), as PD patients with mixed anxiety and depression may respond differently to antidepressants (14, 16).

In the longitudinal study presented in **Chapter 3**, we found an association between anxiety and other neuropsychiatric symptoms as well: the two-year course of anxiety coincided with the course of PD-related impulsive-compulsive behaviors (ICBs), i.e. punding, hobbyism, walkabout and dopamine dysregulation syndrome (DDS). While we are unaware of other studies demonstrating an association between anxiety and ICBs or impulse-control disorders (ICD), the co-occurrence of ICD and depression has been demonstrated in a previous study in PD patients (17). Given the high co-occurrence of anxiety and depression in PD patients, our findings are not surprising. Just like ICD and depression are thought to be two sides of the same coin (18), there is clinical evidence for a comparable relationship between anxiety and ICD, or ICBs like DDS more specifically. While dopamine agonists can have a positive effect on mood (19), DDS can be a serious adverse effect of dopamine replacement therapy (20). On the other hand, withdrawal of dopamine agonists or wearing-off can cause anxiety and depression in PD patients (20, 21). ICD and anxiety / depression may therefore act like communicating vessels, with a decrease in one leading to an increase in the other. This poses difficulties in the pharmacological treatment of motor symptoms in PD patients with a vulnerability for ICD.

In **Chapter 3**, we did not only find an overlap in neuropsychiatric symptoms, but also identified risk factors for anxiety in PD patients, namely cognitive failure and RBD. Executive dysfunction, which is prevalent in PD-related cognitive decline, results in a decreased capacity to respond to challenging environmental situations. This can cause feelings of anxiety or panic in PD patients that are confronted with unexpected events, complex tasks or an excess of stimuli. The role of cognitive dysfunction in anxiety in PD patients is recognized in clinical practice, and supported by the finding that treatment with rivastigmine can have a positive effect on anxiety in PD patients with Mild Cognitive Impairment (MCI) (22).

In this thesis, we were specifically interested in the directionality of the relationship between anxiety, depression and sleep in PD patients. In **Chapter 3**, we found that RBD was associated with anxiety in PD patients. In the longitudinal study presented in **Chapter 4**, we found that insomnia is a predictor for more severe symptoms of anxiety as well as depression. Both RBD and insomnia may result in decreased sleep quality. Previous studies in non-PD samples have shown that disturbed sleep can lead to altered emotional responses and chronic hyperarousal, facilitating the development of anxiety and depression. Inversely, we found that the more severe baseline symptoms of anxiety and depression are predictors for insomnia in PD patients, as well. Insomnia in PD patients may result from a state of arousal due to cognitive, emotional and physical distress (23), caused by the psychological impact of PD or debilitating PD-related symptoms. Based on the findings presented in **Chapter 4**, we conclude that the relationship between insomnia and depression / anxiety may be bidirectional. This is in line with the findings of the PROPARK study, where a bidirectional relationship between insomnia and depression was observed (24). We hypothesize that both anxiety / depression and insomnia can cause a downward spiral, where one symptom can cause or enhance the other. Moreover, as discussed in the next section, shared underlying pathophysiological mechanisms may contribute to the strong relationship between these symptoms.

The etiology of depression, anxiety and sleep disorders in PD

Depression, anxiety and insomnia in PD all have a multifactorial etiology, including both neurobiological and psychological causal factors. The circadian system may play a central role in the pathophysiology of these disorders in PD.
PD-specific neurodegeneration affects various brain areas involved in mood regulation and sleep-wake homeostasis (25-27). Neuroimaging studies in PD patients demonstrate an association between alterations in mesolimbic dopaminergic, serotonergic and noradrenergic systems and symptoms of anxiety and depression (26). The clinical expression of non-motor symptoms throughout the different stages of PD may be a better reflection of the underlying neurodegenerative process than the motor symptoms, which are not manifested before the intermediate stages of PD as defined by Braak, when about 50% of the dopaminergic cells in the substantia nigra have already degenerated (28). Therefore, PD researchers have taken a recent interest in the identification of non-motor subtypes of PD, relating clusters of non-motor symptoms to neuropathological characteristics such as neuronal loss in the limbic and brainstem areas (29). Recent studies have identified a PD phenotype associated with cognitive impairment and psychiatric symptoms (29, 30). Our finding of an association between cognitive failure and anxiety, presented in **Chapter 4**, corresponds to this non-motor phenotype.

As described in **Chapter 6**, as well as in other recent reviews (31, 32), PD-specific neurodegeneration, dopaminergic treatment and conflicting *zeitgeber* input to the circadian system, may all contribute to circadian dysfunction in PD patients. This is reflected in changes in physiological markers of circadian function, like secretion patterns of melatonin and cortisol, but also in behavioral markers, like the sleep-wake cycle. Serotonin, noradrenalin and dopamine all have a circadian rhythm in their release, synthesis-related enzymes and the expression and activity of their receptors (33). It is therefore conceivable that a disturbed circadian rhythm can have a negative impact on both PD-related motor and non-motor symptoms (31, 32). While **Chapter 6** reviews the scientific evidence available up to 2012 for the role of circadian dysfunction in depression and sleep disorders in PD, our own study findings presented in **Chapter 9** provide indirect evidence for a contribution of circadian dysfunction to the pathophysiology of sleep disorders in PD. In this RCT, the group receiving BLT showed a decrease in total salivary cortisol secretion from baseline to the end of treatment. As this group also showed a significantly larger increase in subjective sleep quality, we hypothesize that the perceived enhanced sleep quality results from an improvement of circadian function.

Recent research on neurodegenerative disorders suggests that the detrimental effects of circadian dysfunction may stretch further than the symptomatic level. In a review by Videnovic et al. (2014) on circadian rhythms in neurodegenerative disorders, the authors hypothesize that the relationship between circadian dysfunction and neurodegeneration may be bidirectional: neurodegeneration may cause circadian disruptions, but circadian alterations might trigger and drive neurodegeneration as well, resulting in a self-perpetuating cycle of neurodegeneration and circadian disruption (32). This makes the circadian system an import topic of research in PD patients.

When considering the evident role of the neurodegenerative process in motor and non-motor symptoms in PD patients it is tempting to reduce neuropsychiatric symptoms in PD to consequences of neurochemical dysfunctions. However, all psychiatric disorders have a multifactorial etiology and result from both biological and psychosocial factors. Having a neurodegenerative disorder like PD is accompanied by psychological distress. Being diagnosed with a progressive, incurable disease like PD can cause worries about future disease progression. In advanced stages of PD, treatment-related side effects, including motor response fluctuations, and levodopa-resistant motor symptoms emerge (34). So, at some point in the course of the disease, all PD patients are confronted with the unpredictability of the disease, loss of health and independence, and changes in social identity and role (35, 36). Difficulties with psychosocial adjustment to PD can contribute to the development of clinically relevant symptoms of anxiety and depression (37-39). In **Chapter 3**, we found that the two-year course of symptoms of depression and ICBs was related to the course of anxiety, with more severe symptoms at baseline and a decrease of these neuropsychiatric symptoms during the follow-up period. Since we studied a cohort of *de novo* PD patients, we hypothesized that the high level of symptoms of anxiety, depression and ICBs at baseline represent a reaction to the recent diagnosis of PD. The subsequent decrease of these neuropsychiatric symptoms over the course of two years might be attributable to a successful psychological adjustment over time. As our analyses were corrected for the initiation of antiparkinsonian and psychopharmacological agents, we believe that these findings underline the importance of psychosocial factors in both the development and recovery of neuropsychiatric symptoms in PD.

Methodological considerations

We discussed the specific strengths and limitations of each study in the individual chapters. A major overall strength of this thesis is that we used different study designs, using various statistical techniques in different PD populations, to gain a better understanding of the complex relationship between PD-related motor and non-motor symptoms, especially anxiety, depression and sleep disorders. While the existing scientific evidence of risk factors for neuropsychiatric disorders in PD was mainly based on cross-sectional studies, we studied predictors of anxiety, depression and insomnia in a longitudinal study design in **Chapter 3 and 4**, which allowed us to draw inferences on the temporal relationship of these disorders. The large sample sizes in **Chapter 2, 3 and 4** statistically allowed us to explore a large set of possible predictors, and to correct for various confounders. Another important strength of this thesis is that we studied the effects of LT on PD patients in a RCT design, providing level IB evidence – the second highest level of scientific evidence for the effects of an intervention according to the Oxford Centre for Evidence-based Medicine (40). The results of both RCTs, presented in **Chapter 7 and 9,** indicate that LT has a positive effect on non-motor symptoms in PD patients.

Of course, the studies presented in this thesis also have methodological limitations. First of all, the eligibility criteria of the study population decrease generalizability of our study results. In **Chapter 3 and 4** we used data from the PPMI cohort, a population of *de novo* PD patients. There was probably a selection bias in this study, as clinically relevant symptoms of anxiety and depression were less common in this population than in other prevalence studies (41, 42). In **Chapter 3**, we excluded participants using psychopharmacological agents at baseline, while only PD-medication-naïve participants were eligible for the study presented in **Chapter 4**. The results of these studies can therefore not be generalized to PD patients with more severe neuropsychiatric symptoms or to patients in more advanced disease stages.

Rating scales for psychiatric symptoms show poor clinimetric properties, reliability and validity when used in a population of PD patients, and therefore are of limited use in clinical practice (43, 44). Moreover, since motor symptoms can strongly fluctuate in severity, the UPDRS and MDS-UPDRS might not be able to fully capture the longitudinal effects of LT on motor symptoms. The limitations of the instruments used in our studies may therefore have resulted in over- as well as underestimation of prevalence rates and treatment effects.

The biggest challenge of the RCTs on the effects of LT in PD presented **Chapter 7 and 9**, was to find a reliable control condition. In **Chapter 8**, we already discuss how the appearance of the control device or the characteristics of the emitted light can provide a study participant with clues about the treatment condition. In the studies presented in **Chapter 7 and 9**, we used control devices with a light intensity of 100 and 200 Lux, respectively. However, a study by Zeitzer et al. (2000) suggests that dim light of approximately 100 lux may already cause a shift in circadian rhythm (45), and Colombo et al. (2000) found that a dim 150-lux light condition and bright 2500-lux white light were equally effective in preventing relapse of depressive symptoms after recovery of sleep in sleep-deprived patients with a bipolar disorder (46). Although the participants in the study by Zeitzer et al. (2000) were exposed to LT for several hours instead of 60 minutes daily (45), and the treatment with LT in the study by Colombo et al. (2000) aimed at preventing a relapse of depression instead of reducing current depressive symptoms (46), we cannot rule out the possibility that the light emitted by our control devices influenced the circadian system of the participants in the control groups. Moreover, according to the *social zeitgeber hypothesis,* regulation of the sleep-wake rhythm due to fixed timing of LT may have contributed to a positive effect on sleep and mood. The potential therapeutic effects of our control condition may have led to an underestimation of the efficacy of LT on PD-related symptoms in our trials.

Implications for clinical practice

Diagnosis of neuropsychiatric disorders in PD patients

While there is a risk for underdiagnosis of mental illness due to the incorrect attribution of neuropsychiatric symptoms to other PD-related disturbances like motor or autonomic failure, an "inclusive approach" when rating possible symptoms of anxiety or depression in PD patients carries the risk of overconsumption of health care and unnecessary treatment with potential adverse effects (43, 44, 47). The screening for psychiatric disorders in daily clinical practice can usually be facilitated by the use of questionnaires, but as discussed before, their validity and reliability in PD patients is limited (44). Likewise, Leentjens et al. (2011) have questioned the validity of the classification of psychiatric disorders according to the Diagnostic and Statistical Manual of mental disorders (DSM) in PD patients, as a large proportion of PD patients with clinically relevant psychiatric symptoms in their study did not meet criteria for a specific DSM-IV classification (9). In routine clinical care, results of screening instruments for psychiatric symptoms therefore need to be interpreted with caution before drawing any conclusions on mental health in PD patients. Psychiatric or psychological treatment should be considered in PD patients reporting psychiatric symptoms that cause clinically significant distress or impairment of daily functioning, even if not all DSM criteria for a specific psychiatric disorder are met.

During the diagnostic process, the interaction between PD-related symptoms should be taken into account. A textbook example of this interaction is the phenomenon of wearing-off related anxiety or depression. Wearing-off is defined as "the recurrence of symptoms, that precedes scheduled doses of antiparkinsonian medications and usually improves after those doses" (48). Wearing-off can be accompanied by motor as well as non-motor symptoms, including symptoms of depression and anxiety (21). Patients sometimes describe this form of wearing-off as a feeling of getting "locked into their own body" due to increasing rigidity and bradykinesia, which can be accompanied by strong feelings of fear and helplessness. While this form of non-motor wearing-off can have an impressive clinical presentation, with severe symptoms including panic attacks and suicidality, they disappear after the next dose of dopaminergic medication takes effect. A patient presenting with these wearing-off related psychiatric symptoms could therefore be easily misdiagnosed with a panic disorder or MDD, implicating treatment with an antidepressant, while these symptoms can be reduced by optimization of dopaminergic treatment, improving motor function as well. When diagnosing neuropsychiatric disorders in PD patients, it is therefore essential to inquire about the relationship between neuropsychiatric symptoms and the motor state, to also include a hetero-anamnesis, or to evaluate a patient both in the ON and OFF state.

In general, the diagnostic process of neuropsychiatric disturbances in PD patients is a time-consuming and complex process, requiring expertise from both a psychiatrist and a neurologist. When there is a suspicion of a neuropsychiatric disorder during a neurological evaluation, it is therefore advisable to refer the patient to a psychiatrist for further assessment, preferably one who has clinical experience with PD patients.

Treatment of PD patients

There is still room for improvement when it comes to evidence-based treatment and interdisciplinary collaboration in the care for PD patients suffering from neuropsychiatric disorders. Studies indicate that one to two out of three PD patients with MDD do not receive any form of antidepressant treatment (49, 50). This is partially due to the fact that these patients are not referred to a psychiatrist or psychologist by their treating physician (51). A review by Ouwens et al. (2005) shows that delivery of coordinated and integrated multidisciplinary care, centered around an individual patient with a chronic illness, positively affects clinical outcome, patient functioning and quality of life (52). The results of this thesis underline the importance of multidisciplinary treatment of PD patients by demonstrating the reciprocal influence of PD-related motor and non-motor symptoms. The different health problems associated with PD require collaborative care from different (para)medical professionals. For instance, if a PD patient presents at the neurologist's office with fear of falling, resulting in avoidance of leaving the house alone, interventions from different disciplines may be beneficial. While motor function may improve with an increase in dopaminergic medication, a physical therapist can ameliorate balance with specific exercises, an occupational therapist can enhance mobility with a walker, and anxiety and avoidance may be addressed with psychotherapy.

Neuropsychiatric symptoms are the main determinants of the overall quality of life of PD patients (53). In line with this, in the study presented in **Chapter 6**, we found that health-related quality of life improved with a LT-induced reduction of neuropsychiatric symptoms. Unfortunately, to date, there are no PD-specific guidelines for the treatment of neuropsychiatric disorders, and treatment studies on the effects of psychological and psychopharmacological interventions on symptoms of psychological distress in PD patients are limited, as described in **Chapter 5**. Many PD patients express a preference for non-pharmacological treatment in clinical practice, as antiparkinsonian medications need to be used several times a day to control motor symptoms, and pharmacotherapy is associated with unfavourable side effects. Therefore, this thesis focused on psychological interventions and LT as treatment options for depression and other forms of psychological distress in PD patients. The meta-analysis presented in **Chapter 5** shows that CBT and MBTs have a positive effect on psychological distress in PD patients. The RCT in PD patients without psychiatric comorbidity presented in **Chapter 7** demonstrates a significant effect of Spectramax LT on neuropsychiatric symptoms, including depressive symptoms. However, **Chapter 9** shows that BLT was not superior to a control condition in reducing depressive symptoms in a PD population with MDD. Therefore, we cannot recommend the use of LT in the treatment of depression in PD patients at this stage. Our study findings, do, however, suggest that both Spectramax LT and BLT have a positive effect on sleep in PD patients. **Chapter 9** demonstrated that subjective sleep quality improved in both the experimental and control group, but significantly more in the group receiving BLT. In **Chapter 7**, we describe a trend effect of Spectramax LT on excessive daytime sleepiness (EDS). These findings are in line with the results of a recently published RCT from Videnovic et al. (2017), where LT led to a significantly larger improvement of EDS and self-reported sleep quality in PD patients (54). Based on the present scientific evidence, and the fact that LT is generally well-tolerated, we feel that LT can be considered as a treatment option in PD patients that experience EDS or poor sleep quality at night.

Future directions for research

The study findings presented in this thesis contribute to the knowledge of anxiety, depression and sleep disorders in PD. However, more research needs to be done to fully understand the etiology of these non-motor symptoms, to improve their diagnosis, and to develop PD-specific evidence-based treatment options.

As discussed before, there is a lack of rating scales for psychiatric symptoms that have sufficient validity and reliability in PD patients. In **Chapter 2**, we found that within the BAI an affective subscale can be defined. Since the score on this subscale is not associated with scores on scales assessing motor symptoms and autonomic failure, it might provide a more accurate measure of anxiety in PD than the total BAI, as it is not influenced by physical symptoms that might be either somatic anxiety equivalents or PD-related autonomic or motor symptoms. It would be interesting to assess the sensitivity and specificity of the affective subscale of the BAI in a future study, as it might prove more useful in the screening for anxiety in PD patients than the total BAI. However, the desire to label symptoms as either 'psychiatric' or 'somatic' stems from a physician-centered point of view. From a patient's perspective, an attempt to make a distinction between the emotions, cognitions and somatic sensations, may not correspond to their subjective experience. The differences in viewpoint on the psychosomatic concept of anxiety in PD between a physician and patient may therefore result in physician – patient miscommunication, which is a recognized problem in current clinical care for PD patients. For example, while wearing-off is under-recognized in a substantial number of PD patients during clinical assessment by a neurologist (55), Matthews et al. (2015) demonstrated that the medical explanation for wearing-off cannot be reproduced by the majority PD patients suffering from wearing-off (56). To improve the diagnostic process and provide effective treatment, increased knowledge of the perspective of PD patients on their disease is of importance. To address this, our study group is currently writing the study protocol of a qualitative study, titled '*ParkSpective*', which uses a thematic analysis to assess the experience of PD from the patient's perspective. In the *ParkSpective* study, we aim to gain more insight in the subjective experience of PD patients, and the relevant somatic, emotional, social and societal factors that influence both the perception of and coping with PD. In this study, we will compare physicians' and patients' interpretation of verbal and written expressions from PD patients about their perception of having PD and experiencing its related symptoms. By describing the similarities and differences in point of view, we hope to contribute to an improvement in physician – patient communication.

As health care is moving from physician-centered to patient-centered care (57), personalized medicine gains increasing scientific attention. The identification of phenotypes, or subtypes, of PD may help a physician in predicting disease course and applying more personalized prevention and treatment strategies, as is increasingly possible in the care for MS patients (58). Clinical subtypes of PD can be identified using cluster analysis, as has been done in the study by van Balkom et al. (2016) (59). However, to assess the prognostic reliability of these symptom clusters, large prospective cohort studies, like PPMI, are of major importance. In PPMI, prospective data on clinical characteristics, neuroimaging, biospecimen and genetic information is collected in *de novo* PD patients as well as matched healthy matched controls (60). These data can be used for cluster analyses at different time points during follow-up, but also for the calculation of prediction models using regression analysis. Since previously identified motor subtypes, i.e. tremor dominant versus postural instability gait difficulty (PIGD), are quite unstable over the first years of PD (61), the subtypes based on non-motor symptoms may prove to be more useful for future research.

In parallel, to obtain more insight into the individual needs of persons with PD, n = 1 studies could be of use. As demonstrated in **Chapter 3 and 4**, there is a bidirectional relationship between anxiety, depression and sleep disorders in PD patients. Presumably, the pathway from neuropsychiatric symptoms to sleep disorders and vice versa varies between patients, with one PD patient being more vulnerable for insomnia due to psychological distress, and another developing a psychiatric disorder after many nights of poor sleep. Longitudinal associations between symptoms, both short- and long-term, can be analysed using network analysis. Mulders and colleagues recently used this statistical technique to assess the temporal associations between motor and mood symptoms in a single PD patient, using data collected with an experience sampling method (data not published yet). This type of analysis could also be used to elucidate the pathway to the development of psychiatric or sleep disorders in individuals with PD.

We already emphasized the importance of clinical trials of (non)pharmacological interventions for neuropsychiatric disorders in PD patients, in RCTs with a higher methodological quality and larger study samples. In line with our clinical recommendation of providing multidisciplinary care for PD patients, our study group is currently studying a novel integrative treatment approach for wearing-off related anxiety, combining interventions from physical therapy and psychotherapy in a body-awareness training called *BEWARE* (62). We also would like to encourage further research on the circadian system and the effects of LT in PD patients. The RCTs presented in Part 2 of this indicate that LT has a positive effect on sleep in PD patients. As discussed in **Chapter 9**, the positive effect on subjective sleep quality may be attributable to a normalization of circadian function, as reflected in a decrease in salivary cortisol concentration in the BLT group. However, the mechanisms underlying the positive effects of LT are still largely unclear and need to be elucidated in further experimental studies. Likewise, we would like to explore the factors contributing to the large effects on sleep and mood seen in our control condition. In a *post hoc* analysis that was not presented in **Chapter 9**, we calculated the number of responders in the control group, with 'response' defined as a decrease in HDRS score between baseline and the end of treatment of at least 50%. The percentage of responders in the control group was 44.1%, which is higher than the the average placebo response rate in antidepressant trials (63). As discussed before, our control condition may have had an unanticipated therapeutic effect on mood, either due to a direct influence on the circadian system, or due to an indirect effect, via the regulation of the sleep-wake rhythm or an improvement of sleep quality. To disentangle the effects of sleep-wake regulation and LT, a future RCT ideally would have four treatment groups: i) active LT at set times, ii) biologically inactive LT at set times, iii) LT at random times, iv) biologically inactive LT at random times. Given the paucity of efficacious treatments for neuropsychiatric disorders in PD, and the safety and therapeutic benefits of both LT and sleep-wake regulation, it is interesting to establish what the therapeutic components of our control condition are.

Final conclusions

In *Part 1* of this thesis, we found that there is an overlap between anxiety and symptoms of motor and autonomic failure, and a co-occurrence of anxiety with depression and ICBs. Cognitive failure and RBD were identified as risk factors for the development of anxiety over time. Anxiety/depression and insomnia have a bidirectional relationship in PD patients. The complex relationships between motor and non-motor symptoms in PD warrant a multidisciplinary approach of persons with PD for both diagnosis and treatment. The etiology of anxiety, depression and sleep disorders in PD patients is multifactorial, with both neurobiological and psychological causal factors. The circadian system may play a central role in the development of these disorders, providing an interesting target for treatment with chronotherapeutic interventions like LT. In *Part 2* of this thesis, we presented two RCTs, demonstrating the positive effects of LT on non-motor symptoms in PD patients. As BLT was not more effective in the treatment of depression in PD patients with MDD than a control LT device, we cannot recommend BLT as a treatment option for depression in PD at this point. However, we did find positive effects of LT on subjective sleep quality and daytime sleepiness, indicating that LT can be considered as a treatment option in PD patients who experience sleep disturbances.

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A

Appendix

Nederlandse samenvatting (Dutch summary)
Dankwoord (Acknowledgements)
About the author
List of publications
Dissertation Series

Nederlandse samenvatting (Dutch summary)

De ziekte van Parkinson is een neurodegeneratieve aandoening die bij 1.350 op de 100.000 Nederlanders voorkomt. De ziekte staat bekend om de kenmerkende bewegingsklachten oftewel motorische symptomen: beven, stijfheid, traagheid, een verstoorde balans en een afname van spontane bewegingen en mimiek. De ziekte gaat echter ook gepaard met een scala aan niet-motorische symptomen, zoals stoornissen van het autonome zenuwstelsel (problemen met de temperatuur- en bloeddrukregulatie, blaas, darmen en seksuele functies), het cognitief functioneren (het denken en geheugen), de slaap en het psychisch functioneren.

Psychiatrische stoornissen die voor komen bij de ziekte van Parkinson zijn onder andere psychose, apathie, angststoornissen, depressie en impulscontrolestoornissen. Deze psychiatrische aandoeningen worden veroorzaakt door een combinatie van biologische, sociale en psychologische factoren. Zo zijn angst en depressie een begrijpelijke reactie op het krijgen van de diagnose ziekte van Parkinson: een ongeneeslijke ziekte, die in toenemende mate tot beperkingen leidt. Biologische factoren spelen echter ook een belangrijke causale rol. Uit studies waarbij gebruik wordt gemaakt van beeldvormende technieken komt naar voren dat de neurobiologische veranderingen ten gevolge van het neurodegeneratieve proces ook geassocieerd zijn met psychiatrische symptomen. Hiernaast lijken parkinsonpatiënten door verschillende factoren gevoelig te zijn voor een verstoring van het circadiane systeem. Het circadiane systeem zorgt dat ons innerlijke bioritme synchroon loopt met het 24-uurs ritme van de maatschappij. Een verstoring van het circadiane systeem kan tot slaapproblemen en depressieve klachten leiden, zoals bijvoorbeeld ook bij mensen met een winterdepressie wordt gezien.

Veel parkinsonpatiënten hebben slaapproblemen, variërend van overmatige slaperigheid overdag tot slapeloosheid. Ook specifieke slaapstoornissen, zoals de REM-slaap gedragsstoornis, komen vaker voor bij patiënten met de ziekte van Parkinson, dan in de algemene bevolking. Ongeveer één op de drie parkinsonpatiënten ontwikkelt tijdens het beloop van de ziekte een angststoornis en 17% een depressie. Hiernaast heeft een aanzienlijk deel van de parkinsonpatiënten angst- of depressieve klachten, zonder dat deze voldoen aan de diagnostische criteria voor een psychiatrische aandoening in engere zin. Angst en depressie hebben een grote negatieve impact op het functioneren en de kwaliteit van leven van parkinsonpatiënten en hun mantelzorgers.

Dit proefschrift richt zich voornamelijk op angst, depressie en slaapproblemen bij de ziekte van Parkinson. In **Hoofdstuk 1** wordt een algemene inleiding hierover gegeven, en worden de doelstellingen van dit proefschrift toegelicht.

Bij parkinsonpatiënten komen angst en depressie vaak gelijktijdig voor, en is in meerdere onderzoeken een relatie met slaapproblemen gevonden. De diagnostiek van deze psychiatrische aandoeningen wordt echter bemoeilijkt door een overlap en interactie met andere parkinson-gerelateerde klachten. Het doel van het eerste deel van dit proefschrift (**Hoofdstuk 2 t/m 4**) was daarom meer inzicht te krijgen in angst, depressie en slaapproblemen bij patiënten met de ziekte van Parkinson, hun onderlinge relatie, en de associatie met andere parkinson-gerelateerde symptomen.

In **Hoofdstuk 2** onderzochten we de verschillende symptoomdimensies van angst in een groep van 294 parkinsonpatiënten. Angst werd gemeten met een vragenlijst, de Beck Anxiety Inventory (BAI). De items van de BAI werden in deze studie met een factoranalyse onderverdeeld in subschalen of 'symptoomdimensies'. Hierbij vonden we vier 'somatische' subschalen, die lichamelijke sensaties meten, en één 'affectieve'subschaal, die items over angstige gedachten en emoties bevat. Toen we keken naar de relatie van deze subschalen met andere parkinson-gerelateerde klachten, vonden we dat alle subschalen een associatie hadden met de score op een meetinstrument voor depressie. Dit bevestigt de eerder gevonden sterke relatie tussen angst en depressie bij parkinsonpatiënten. We vonden ook een associatie tussen de somatische subschalen en de score op meetinstrumenten die autonome functiestoornissen en motorische symptomen meten, terwijl deze associatie bij de affectieve subschaal niet aanwezig was. Dit suggereert dat de affectieve subschaal van de BAI een meer accurate maat voor angst zou kunnen zijn bij parkinsonpatiënten, omdat hierbij geen 'ruis' ten gevolge van lichamelijke klachten ontstaat. Een scheiding tussen angst en lichamelijke symptomen zou in de praktijk echter kunstmatig zijn, aangezien bij patiënten met de ziekte van Parkinson bekend is dat angst en lichamelijke klachten met elkaar verweven zijn. Angst en motorische klachten kunnen elkaar veroorzaken en versterken, maar zich ook met vergelijkbare symptomen presenteren.

Aangezien de diagnostiek van angst complex is, zouden parkinsonpatiënten met angstklachten in de dagelijkse praktijk mogelijk beter herkend worden als er meer bekend is over de risicofactoren voor angst. In **Hoofdstuk 3** presenteren we de resultaten van een longitudinaal onderzoek naar voorspellers van angst bij een groep van 306 patiënten die recent gediagnosticeerd zijn met de ziekte van Parkinson. Er werden vier predictoren gevonden: depressie, symptomen van impulscontroleproblematiek, cognitieve functiestoornissen en de aanwezigheid van een REM-slaapgedragsstoornis. Het beloop van depressie en impulscontroleproblematiek was gelijk aan dat van angst: er waren meer klachten bij aanvang van het onderzoek, en deze klachten namen af gedurende de twee jaar follow-up. Dit zou verklaard kunnen worden door een psychologische reactie op de diagnose, gevolgd door een emotionele aanpassing in de loop van de tijd. De aanwezigheid van cognitieve problemen bleek een risicofactor te zijn voor een toename van angstklachten gedurende follow-up. Dit zou verklaard kunnen worden door een verminderd vermogen om flexibel te reageren op stressvolle gebeurtenissen in de directe omgeving, ten gevolge van cognitieve functiestoornissen. Tenslotte was de aanwezigheid van een REM-slaapgedragsstoornis een voorspeller van een toename van angst. Een mogelijke verklaring hiervoor is een kwalitatief slechtere nachtrust ten gevolge van de slaapstoornis. Uit onderzoek is gebleken dat slechte slaap een negatieve impact heeft op het vermogen om emoties te reguleren, wat het risico op het ontwikkelen van angstklachten kan vergroten. Een laatste mogelijke verklaring voor de gevonden associaties is dat er een uitgebreider onderliggend neurodegeneratief proces speelt bij patiënten met zowel cognitieve problemen, slaapproblemen en psychische klachten; hier zijn aanwijzingen voor gevonden in beeldvormend en neuropathologische studies.

In **Hoofdstuk 2 en 3** werd een relatie tussen depressie, angst en slaapproblemen bij de ziekte van Parkinson gevonden. In **Hoofdstuk 4** hebben we de temporele relatie tussen deze klachten nader bestudeerd. In een cohort van 361 parkinsonpatiënten vonden we dat de relatie bi-directioneel is: patiënten met ernstiger klachten van angst en depressie hadden een hogere kans op slapeloosheid, en vice versa was de aanwezigheid van slapeloosheid bij aanvang van de studie een voorspeller voor ernstiger klachten van angst en depressie na een half jaar. Wij vermoeden dat zowel angst / depressie als slapeloosheid een negatieve spiraal kunnen veroorzaken, waarbij de ene klacht de andere kan veroorzaken en versterken.

In het tweede deel van dit proefschrift wordt de aandacht verlegd van diagnostiek naar behandeling. Bij de medicamenteuze behandeling van slaapproblemen, angst of depressie bij parkinsonpatiënten bestaat er een risico op bijwerkingen, zoals een verhoogd valrisico. Daarnaast geven veel parkinsonpatiënten aan dat zij een voorkeur hebben voor niet-medicamenteuze behandeling, omdat zij al veel medicatie moeten slikken om de symptomen van de ziekte van Parkinson tegen te gaan. Daarom is er een toenemende interesse voor niet-medicamenteuze behandelvormen. In het tweede deel van dit proefschrift (**Hoofdstuk 5 t/m 9**) richten wij ons dan ook op niet-medicamenteuze behandelopties voor parkinsonpatiënten.

In **Hoofdstuk 5** presenteer ik de resultaten van een meta-analyse naar het effect van twee psychologische interventies, cognitieve gedragstherapie en minfulness-based therapie, op psychologisch welbevinden bij patiënten met drie verschillende neurodegeneratieve aandoeningen: de ziekte van Parkinson, Multipele Sclerose en de ziekte van Huntington. We vonden geen onderzoeksresultaten van gerandomiseerd, gecontroleerd onderzoek bij patiënten met de ziekte van Huntington. De studies in patiënten met de ziekte van Parkinson en Multipele Sclerose waren over het geheel genomen van onvoldoende methodologische kwaliteit, maar lieten een klein tot matig therapeutisch effect zien, wat suggereert dat psychologische interventies een positief effect kunnen hebben op psychologisch welbevinden in deze patiëntengroepen.

In **Hoofdstuk 6** introduceren we lichttherapie als niet-medicamenteuze behandeloptie voor slapeloosheid en depressie bij de ziekte van Parkinson. In dit literatuuroverzicht beschrijven we hoe het circadiane systeem bij parkinsonpatiënten door diverse factoren negatief beïnvloed wordt, waarbij er een desynchonisatie van het circadiane ritme ten opzichte van het 24-uurs ritme van de maatschappij kan optreden. Bij diverse onderzoeken onder parkinsonpatiënten is een faseverschuiving en afvlakking van markers van het circadiane ritme gevonden. Wij vermoeden dat deze circadiane verstoringen een belangrijke causale factor vormen in het veelvuldig optreden van slaapproblemen en depressie bij de ziekte van Parkinson. Lichttherapie kan het circadiane ritme herstellen, en vormt zo een potentiële niet-medicamenteuze behandeloptie voor slaapproblemen en depressie bij parkinsonpatiënten. Eerdere studies naar dit onderwerp bevestigen de positieve effecten van lichttherapie op slaap, stemming en motorisch functioneren bij parkinsonpatiënten. Gerandomiseerd, gecontroleerd onderzoek naar de effecten van lichttherapie bij de ziekte van Parkinson ontbrak echter nog. In de laatste hoofdstukken van dit proefschrift hebben wij ons hier op gericht.

In **Hoofdstuk 7** beschrijven we de resultaten van een door de industrie-geïnitieerd multicenter, dubbelblind gerandomiseerd onderzoek naar de effectiviteit en veiligheid van Spectramax lichttherapie als adjuvante behandeling voor de ziekte van Parkinson. We randomiseerden 92 parkinsonpatiënten naar behandeling met Spectramax lichttherapie of controle-lichttherapie. De Spectramax lichttherapie-lamp straalt 950 Lux groen/blauw licht uit met een specifieke golflengte, waarvan werd verwacht dat deze specifiek relevant was voor parkinsonpatiënten. Van de controle lichttherapie-lamp werd geen effect op het circadiane ritme verwacht. Deelnemers werden gedurende een half jaar dagelijks een uur behandeld in de thuissituatie. Aan het einde van de behandelperiode vonden we geen verschil tussen beide behandelcondities in de primaire uitkomstmaat, de somscore van deel I, II en III van de Movement Disorders Society – Unified Parkinson's Disease Rating Scale, wat een maat is voor de ernst van motorische en niet-motorische symptomen van de ziekte van Parkinson. Wel zagen we een grotere afname van niet-motorische symptomen, inclusief psychiatrische klachten, in de groep die met Spectramax lichttherapie werd behandeld, evenals een sterkere verbetering van de kwaliteit van leven en een trend-effect op overmatige slaperigheid overdag. Behandeling met Spectramax lichttherapie gaf geen klinisch relevante bijwerkingen en werd over het algemeen goed verdragen. Deze resultaten suggereren dat Spectramax lichttherapie mogelijk een positief effect kan hebben op niet-motorische symptomen, waardoor verder onderzoek hiernaar zinvol wordt geacht.

In **Hoofdstuk 8** beschrijven we het onderzoeksprotocol van een door ons eigen onderzoeksteam geïnitieerd dubbelblind, gerandomiseerd onderzoek waarin we het effect van lichttherapie op depressie bij de ziekte van Parkinson vergelijken met een controleconditie. Deelnemers aan dit onderzoek hadden de ziekte van Parkinson en een depressieve stoornis. Zij werden gedurende drie maanden 's ochtends en 's avonds een half uur behandeld met lichttherapie (wit licht, 10.000 Lux), of een controle-licht (gedimd wit licht, 200 Lux) waarvan geen effect op het circadiane systeem werd verwacht. In beide groepen vond slaap-waak structurering plaats doordat de deelnemers in de ochtend op een vaste tijd opstonden om lichttherapie te volgen, en ongeveer een uur na de avond-lichttherapie naar bed gingen. De primaire uitkomstmaat was de ernst van de depressie, gemeten met de Hamilton Depression Rating Scale. Secundaire uitkomstmaten waren onder andere slaap en de concentraties van melatonine en cortisol in speeksel, welke beiden markers zijn voor het circadiane ritme.

In **Hoofdstuk 9** presenteren wij de resultaten van deze studie. In beide onderzoeksgroepen trad een duidelijke verbetering van de stemming en slaap op. Een combinatie van slaap-waak structurering en lichttherapie leidde echter niet tot een statistisch significant grotere vermindering van depressieve klachten, dan een combinatie van slaap-waak structurering en controle-lichttherapie. Op basis van deze studie kunnen wij lichttherapie dus niet adviseren als behandeling voor depressie bij parkinsonpatiënten. Desalniettemin herstelde 44% van de deelnemers in de controlegroep en 56% in de lichttherapie-groep van zijn/haar depressie. Wij vermoeden dat de afname van depressieve klachten die we in beide groepen zagen, deels verklaard wordt door een placebo-effect, en deels door een verbetering van het slaap-waak ritme. Er was wel een significant verschil tussen beide groepen in de ervaren slaapkwaliteit aan het einde van de behandelperiode: deze verbeterde meer in groep die met lichttherapie behandeld werd, dan in de controlegroep. Daarnaast lieten de patiënten die lichttherapie hadden gehad ten opzichte van de controlegroep een significante verlaging in de cortisolconcentratie zien na behandeling. Wij denken dan ook dat de verbetering van de slaapkwaliteit in deze groep een gevolg was van de afname in cortisolsecretie onder invloed van lichttherapie.

In **Hoofdstuk 10** zijn de bevindingen van dit proefschrift samengevat en becommentarieerd. Ik beschrijf hier hoe er een wisselwerking en overlap bestaat tussen angst, depressie, slaapproblemen en andere parkinson-gerelateerde klachten, wat zowel de diagnostiek als behandeling van deze klachten bij parkinsonpatiënten bemoeilijkt. In dit hoofdstuk voer ik een pleidooi voor een meer geïntegreerd psycho-somatisch concept van de ziekte van Parkinson, en een multidisciplinaire behandeling van parkinsonpatiënten. Daarnaast bespreek ik het nut van nader onderzoek naar de diverse fenotypes van de ziekte van Parkinson, kwalitatieve studies, en n = 1 studies, die een aanknopingspunt kunnen bieden voor een meer gepersonaliseerde behandeling van parkinsonpatiënten.

Ik beargumenteer dat de etiologie van angst, depressie en slaapproblemen bij patiënten met ziekte van Parkinson multifactorieel is, en dat zowel psychologische als biologische factoren, inclusief circadiane ontregelingen, een rol spelen. Aangezien een verbetering van het circadiane ritme een positief effect lijkt te hebben op niet-motorische symptomen bij de ziekte van Parkinson, blijft deze niet-medicamenteuze behandeling een interessant onderwerp voor verder onderzoek.

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About the author

Sonja Rutten was born on the 14th of February 1984 in Groningen, the Netherlands. In 2002 she graduated from the Zernike College in Haren, after which she started her studies of Medicine at the University of Groningen. She did a scientific internship at the Voices Outpatient Department of the University Center of Psychiatry in Groningen, under supervision of dr. Jack Jenner. After finishing her clinical residency in Medisch Spectrum Twente, a hospital in Enschede, she graduated as an MD in 2008.
After one year of working as an MD at both the Voices outpatient department in Groningen, and in a team for Assertive Community Treatment at GGZ inGeest in Amsterdam, Sonja started her residency in psychiatry at GGZ inGeest in 2009. In 2012, she joined the section of Neuropsychiatry, led by prof. dr. Odile van den Heuvel and prof. dr. Ysbrand van der Werf, as a PhD student at the department of Psychiatry and the department of Anatomy and Neuroscience at GGZ inGeest / Amsterdam University Medical Centers (UMC). She studied depressive, anxiety and sleep disorders in patients with Parkinson's disease; the results are presented in this thesis. In 2014, she started a post-doctoral Master in Epidemiology, from which she graduated in 2015.

After finishing her psychiatry residency in 2017, Sonja has worked as a psychiatrist at the MC Zuiderzee hospital in Lelystad, the Netherlands Cancer Institute (Antoni van Leeuwenhoek hospital) in Amsterdam and the department for elderly psychiatry at GGZ inGeest, Amsterdam. She currently works as a psychiatrist at the outpatient department for hospital psychiatry at Amsterdam UMC, location VU University medical center, in Amsterdam.

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